



THE  
AMERICAN JOURNAL  
OF THE  
MEDICAL SCIENCES

EDITED BY  
JOHN H. MUSSER, JR., M.D.  
E. B. KRUMBHAAR, M.D.  
ASSISTANT EDITOR

NEW SERIES

VOL. CLXIV



PHILADELPHIA AND NEW YORK  
LEA & FEBIGER  
1922



COPYRIGHT  
LEA & FEBIGER  
1922

# CONTENTS OF VOL. CLXIV

---

## ORIGINAL ARTICLES

The Actions of Atropine and Quinidine in Fibrillation of the Auricles: Clinical and Experimental Studies. By THOMAS LEWIS . . . .	1
The Phenomena of Raynaud's Disease. By J. ARTHUR BUCHANAN, M.D. .	14
The Spleen and Digestion. Study II. The Spleen and Pancreatic Secretion. By WILLIAM DE P. INLOW, M.S., M.D. . . . .	29
The Surgical Aspects of Disease of the Biliary Tract. By ABRAHAM O. WILENSKY, M.D. . . . .	44
The Etiology of Pneumonia. By RUSSELL L. CECIL, M.D. . . . .	58
The Introduction of Antimeningococcus Serum by Cistern Puncture. Report of a Case of Meningococcus Meningitis in an Infant, Aged Four Months, Cured by this Method. By A. GRAEME MITCHELL, M.D., and J. J. REILLY, M.D. . . . .	66
Report of a Case of Disseminated Gummatous Sporotrichosis, with Lung Metastasis. By LOUIS M. WARFIELD, A.B., M.D. . . . .	72
Comparative Prognosis in Tuberculous Lesions of the Right and Left Lung. A Study of 1048 Cases. By BARNET P. STIVELMAN, M.D., and NATHAN C. MILLER, M.D. . . . .	82
Observations on the Blood in Cases of Chronic Nephritis Associated with Nitrogen Retention. By BENJAMIN N. BERG, M.D. . . . .	88
The Present Status of the Treatment of Hay Fever and Asthma. By A. VANDER VEER, JR., M.D. . . . .	97
Syphilitic Backache. By WARREN THOMPSON, M.D. . . . .	109
The Incidence of Cecal Tuberculosis with Pulmonary Tuberculosis. By I. H. LEVY, M.D., and H. H. HAFT, M.D. . . . .	115
The Action of Digitalis in Case of Auricular Fibrillation and Flutter. By THOMAS LEWIS . . . . .	157

The Spleen and Digestion. Study III. The Spleen in Inanition; the Effect of the Removal of the External Secretion of the Pancreas on the Spleen. By WILLIAM DE P. INLOW, M.S., M.D. . . . .	173
Gastrosplasm: A Clinical and Roentgenological Study. By I. W. HELD, M.D., and J. ROEMER, M.D. . . . .	188
The Best Technic for Gastroenterostomy as Determined by Functional Results. By ABRAHAM O. WILENSKY, M.D. . . . .	209
The Male Sexual Gland in the Prevention of Creatinuria. By MORLEY D. MCNEAL, M.D. . . . .	222
A Clinical and Pathological Study of Neuritis in the Tropics, with Special Reference to Beriberi. By WILLIAM E. MUSGRAVE, M.D., and BOWMAN C. CROWELL, M.D. . . . .	227.
Clinical Differentiation of Epidemic Encephalitis, Acute Poliomyelitis, Botulism and Certain Forms of Food and Drug Poisoning. By GEORGE E. EBRIGHT, M.D. . . . .	253
The Status of Exercise in the Tuberculous Considered from a Neuromuscular Viewpoint. By FRANK PORTER MILLER, M.D. . . . .	263
Postoperative Massive Collapse of the Lungs. By F. J. HIRSCHBOECK, . . . .	268
Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect. By LE ROY H. BRIGGS, M.D. . . . .	275
Infection of the Gastrointestinal Tract in Systemic Disorders: Medical Viewpoint. By G. REESE SATTERLEE, M.D. . . . .	313
Infection of Gastrointestinal Tract in Relation to Systemic Disorders: Surgical Viewpoint. By JOHN W. DRAPER, M.D. . . . .	322
Infection of the Gastrointestinal Tract in Relation to Systemic Disorders: Neurological Viewpoint. By HENRY A. COTTON, M.D. . . . .	329
The Application to Other Institutions of the Results of Treatment of the Insane in Trenton State Hospital. By BURDETTE G. LEWIS. . . . .	338
Carcinoma of the Esophagus with Perforation of the Aorta; Observations on Radium Therapy. . By JAMES G. CARR, M.D., and C. W. HANFORD, M.D. . . . .	340
Notes on Studies in the Physiology of the Gall-bladder. By LIONEL S. AUSTER and BURRILL B. CROHN, M.D. . . . .	345
Chemical Changes of the Blood during Immunization. By G. L. ROHDENBURG, M.D., O. F. KREHBIEL, M.D., and A. BERNHARD, B.S. . . . .	361

Biochemical Studies in Diseases of the Skin. II. Acne Vulgaris. By OSCAR L. LEVIN, M.D., and MAX KAHN, M.D. . . . .	379
The Clinical Importance of Aseptic Infarction of the Kidney. By PAUL W. ASCHNER, M.D. . . . .	386
The Study of Vestibular Nerve Function in Myxedema. By ROY A. BARLOW, M.D. . . . .	401
The Treatment of the Syphilitic Liver and Heart: A Therapeutic Paradox. By UDO J. WILE, M.D. . . . .	415
Acute Lung Abscess Treated by Therapeutic Pneumothorax. By HERBERT M. RICH, M.D. . . . .	428
Clinical Observations on Block of the Branches of the Auriculoventricular Bundle. By JAMES B. HERRICK, M.D., and FRED M. SMITH, M.D. . . . .	469
Post-traumatic Calcification of the Pancreas, with Diabetes. By H. GIDEON WELLS, M.D. . . . .	479
Quantitative Studies in Syphilis from a Clinical and Biologic Point of View. By JOHN A. FORDYCE, M.D., ISADORE ROSEN, M.D., and C. N. MYERS, PH.D. . . . .	492
The Wassermann Reaction in Non-luetic Cases. By T. MCKEAN DOWNS, M.D. . . . .	514
A Further Note upon a Comparison of the Sachs-Georgi and Wassermann Reactions in the Serologic Diagnosis of Syphilis. By ROBERT A. KILDUFFE, M.D. . . . .	523
Treatment of Syphilis among the Insane. By THOMAS B. CHRISTIAN, M.D. . . . .	526
The Roentgen-ray Diagnosis of Tuberculous Cervical Lymph Glands. By JOHN MUNN HANFORD, M.D. . . . .	539
Three Cases of Leukemia in One Family. By CHARLES W. MCGAVRAN, M.D. . . . .	545
The Clinical Significance of Total and Differential Leukocyte Counts, with Special Reference to Acute Infections. By WALTER CLINTON JONES, M.D., and CLARA ENEBIE BROWN . . . . .	553
The Surgery of Thoracic Tumors. By ABRAHAM O. WILENSKY, M.D. . . . .	573
The Diagnosis and Treatment of Amebic Colitis. By ALFRED C. REED, M.D. . . . .	587

Endocrinology as a Key to the Solution of Major Medical Problems. By CHARLES E. DE M. SAJOUS, M.D. . . . .	625
A Résumé of Our Knowledge of the Functions and Interrelations of the Endocrine Glands. By FRANCIS ASHLEY FAUGHT, M.D., and THOMAS J. RYAN, M.D. . . . .	646
Auricular Flutter, with Report of Cases. By JOHN H. KEATING, M.D., and JOSEPH HAJEK, M.D. . . . .	656
Concerning the Wassermann Test in its Relation to Prenatal and Congenital Syphilis. By ROBERT A. KILDUFFE, M.D. . . . .	677
Two Instances of Defective Interventricular Septum of the Heart. By H. W. CAREY, M.D. . . . .	684
The Treatment of Hypertoxic Cases of Typhoid Fever by Transfusion with Recently Artificially Immunized Blood. By LESTER NEUMAN, M.D. . . . .	690
Congenital Absence of the Spleen. By STAFFORD McLEAN, M.D., and HOWARD R. CRAIG, M.D. . . . .	703
Delay in the Treatment of Cancer. By CHARLES E. FARR, M.D. . . . .	712
The Vibrating Sensation in Diseases of the Nervous System. By R. T. WILLIAMSON, M.D. . . . .	715
The Relationship between Central and Peripheral Involvement of the Cranial Nerves. By ERNEST SACHS, M.D. . . . .	727
Orthostatic Albuminuria: The Study of an Unusual Case. By WYNDHAM B. BLANTON, M.D. . . . .	742
Infectious Mononucleosis (Glandular Fever), with a Report of Ten Cases. By WARFIELD T. LONGCOPE, M.D. . . . .	781
The Relations of Hypertension to Cardiorenal Diseases. By NELLIS B. FOSTER, M.D. . . . .	808
Long-continued Observations on the Vital Capacity in Health and Heart Disease. By JOSEPH H. PRATT, M.D. . . . .	819
Experiences in New York Hospital, with the Treatment of Lobar Pneumonia by a Serum-free Solution of Pneumococcus Antibodies. By LEWIS A. CONNER, M.D. . . . .	832
Pregnancy Complicating Heart Disease. By HAROLD E. B. PARDEE, M.D. . . . .	847
The Mechanism of Elimination of Bacteria from the Respiratory Tract. By ARTHUR L. BLOOMFIELD, M.D. . . . .	854

Two Hundred Syphilitic Patients Whose Chief Complaint was "Stomach Trouble"; an Interpretative Analysis of the Diagnosis of Syphilis in Consultant Medical Practice. By JOHN H. STOKES, M.D., and PHILIP W. BROWN, M.D. . . . .	867
The Safeguarding of the Tonsil and Adenoid Operation (the Prevention and Treatment of Some of the Postoperative Complications of this Operation). By GEORGE FETTEROLF, M.D. . . . .	884
Clinical Observations and Research Work. By JOHN B. DEEVER, M.D., and STANLEY P. REIMANN, M.D. . . . .	901

## REVIEWS

Reviews of Books. . . . .	124, 282, 437, 595, 749, 905
---------------------------	------------------------------

---

## PROGRESS OF MEDICAL SCIENCE

Medicine . . . . .	133, 289, 447, 603, 755, 911
Surgery . . . . .	135, 292, 450, 606, 757
Pediatrics . . . . .	139, 296, 454, 610, 760, 915
Obstetrics . . . . .	143, 300, 458, 614, 764, 919
Dermatology and Syphilis . . . . .	923
Gynecology . . . . .	147, 303, 617, 768
Pathology and Bacteriology . . . . .	150, 307, 462, 621, 771, 925
Hygiene and Public Health . . . . .	153, 310, 465, 623, 776, 928

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

JULY, 1922

---

ORIGINAL ARTICLES.

THE ACTIONS OF ATROPINE AND QUINIDINE IN FIBRILLATION OF THE AURICLES; CLINICAL AND EXPERIMENTAL STUDIES.

SECOND LECTURE\*

By THOMAS LEWIS,

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND.

IN studying the action of quinidine upon the fibrillating auricle and in considering the nature of this action, we may conveniently begin by noticing certain effects of vagal stimulation, and certain effects of abolishing vagal tone, upon the mammalian auricle.

For many years it has been customary to regard an increased vagal tone as having a purely depressant effect upon the functions of the mammalian heart muscle. We know that vagal stimulation slows the natural heart beat, produces heart-block at the *A-V* ring, that it notably reduces the force of the auricular contractions and that, under vagal stimulation, the auricle will no longer respond to electric shocks of previously threshold strength. From these observations it has been natural to conclude that the vagus tends to inhibit rhythmic impulse formation in the heart, that it hinders

\* Observations carried out on behalf of the British Medical Research Council at University College Hospital Medical School (London). A Wiley-Noble-Jones Lecture, delivered at the University of Oregon Medical School, Portland, in May, 1922. In this lecture I have utilized much material, as yet unpublished in detail and collected in collaboration with my coworkers, Dr. A. N. Drury, Dr. C. C. Iliescu and Dr. A. M. Wedd.

The third and last lecture will appear in the August issue of this publication; the first lecture appeared in the June issue.



conduction in the heart, and that it reduces the force of the muscular contractions and decreases the excitability of the muscle. We have been tempted to apply all these conclusions to the muscle of the heart generally, and especially to the auricle, in considering the action of the vagus upon forms of auricular disorder. If we are to avoid serious fallacy, we must particularize and avoid transferring a conclusion which applies to one section of heart muscle to a second section. Since vagal stimulation reduces the power of the *A-V* tissues to conduct in the mammalian heart, there would seemingly be little risk in concluding that its action is similar upon the muscle of the auricle itself, for this muscle is known to be powerfully controlled by the inhibitory nerve. But the risk of such conclusions is a grave one, as this example illustrates; recent observation has shown quite clearly that the vagus has not the power to depress auricular conduction. If the mammalian auricle is beating normally, vagal stimulation leaves conduction in this muscle unchanged. Furthermore, if for any reason the rate of conduction is primarily reduced in the auricle, then vagal stimulation exerts a paradoxical effect; it increases the rate of conduction. For the purposes of this lecture we are concerned chiefly with depressed conduction due to an increased rate of beating, such as occurs in flutter and in fibrillation; in the case of conduction slowed by this cause, vagal stimulation brings transmission rates back to normal.<sup>8</sup> The meaning of this becomes clearer if we recognize that this disturbed conduction is connected with the refractory period of the muscle under observation. If a new stimulus falls on the muscle before it has obtained sufficient rest, it finds this muscle only partially recovered; it is partially refractory, and the wave propagated therefore travels slowly. When the vagus is stimulated, the contraction of the muscle is much reduced in amplitude, it is also conspicuously reduced in its duration;<sup>8</sup> the systoles are now very brief and the rest periods between the responses become sufficiently prolonged to permit complete recovery.

Thus, from recent observation come two conclusions: Vagal stimulation (1) conspicuously reduces the length of the refractory period and (2) it quickens conduction in an auricle which is beating rapidly. Section of the vagi, or atropinization,<sup>8 11</sup> have the opposite effects. These two conclusions are of much consequence when we consider the effects of vagal stimulation upon the fluttering or fibrillating auricle.

Our reasons for the belief that auricular flutter and fibrillation are dependent upon a circus movement have been discussed at some length,\* and for the purposes of this lecture I ask you to accept this conclusion. The maintenance of a circus movement in the auricle

\* The nature of flutter and fibrillation was the theme in two preliminary lectures of this series, the ground covered being very similar to that covered by the Oliver-Sharpey lectures<sup>6</sup> of 1921.

depends on certain factors which we may now examine in some detail.

It is essential that as the wave circulates, a gap between its crest and wake should be maintained. Otherwise the crest of the wave, in advancing, will find no responsive muscle ahead of its movement. Upon the existence of this gap, the maintenance of the movement depends absolutely.

*The Length of Gap.* Start a wave in one direction along a circular path. The wave begins at one point, and moves around the circle. The muscle at the starting point becomes refractory or unresponsive as it receives the wave; it remains unresponsive for a given length of time, a period termed the *refractory period*.

The shorter this refractory period, the smaller will be the distance which the wave travels before the starting point again enters the responsive state. The shorter the distance travelled by the wave in a given time, the greater will be the gap left between its crest and the starting point to which it is returning. The distance travelled will be less, the slower the wave moves; a longer gap results therefore from slower conduction. Finally, the longer the path to be travelled by the wave, the longer will be the gap. Thus, the length of gap is determined by three factors:

1. Length of path.
2. Duration of refractory period.
3. Rate of propagation.

Although these three factors obviously *determine* the length of the gap, strictly speaking it is not correct to say that they all control it. The original muscle tract persists unaltered and, so long as the state of conduction and refractory period remain unchanged, the wave will move along it. It is change in one of the last two factors, which can alone alter the original gap. Refractory period and conduction rate alone *control* the gap. But, subject to change in one or other of these factors, the path itself may vary.

This variation is brought about in the following way. Suppose that the refractory period lengthens or the rate of propagation increases, the gap shortens. If from either of these causes the gap *disappears*, the wave does not necessarily cease to circulate; it will continue to circulate if a longer channel is open to it (Fig. 1 *b*). Reversely, if the refractory period shortens, or the rate of propagation decreases, the gap will widen and, in widening, it may open up to the wave a shorter channel, which the wave will then pursue (Fig. 1 *c*). The moment lengthening or shortening of the path occurs, this change will also affect the length of gap; but it is to be emphasized that this change is secondary to change in the remaining factors and consequently becomes of secondary importance theoretically, when changes in the gap are considered. These remarks bring me to discuss our problem in a different manner.

*The Number of Circuits per Minute.* As the wave is continuous, the number of circuits per minute depends solely upon the circulation time. It will be at once evident that the time of circulation is determined by the length of the path and the rate at which the wave travels; refractory period exerts no direct influence. The circulation time will be shorter, and the circuit movements will be more numerous if the path is short and the rate of propagation rapid; conversely, the time will be longer, and the circuit movements fewer, if the path is long and the rate of propagation slow. But refractory period cannot be left out of the account, it is subject to variation; by increasing it can force the wave to travel upon a longer channel, by decreasing it can induce the wave to flow upon

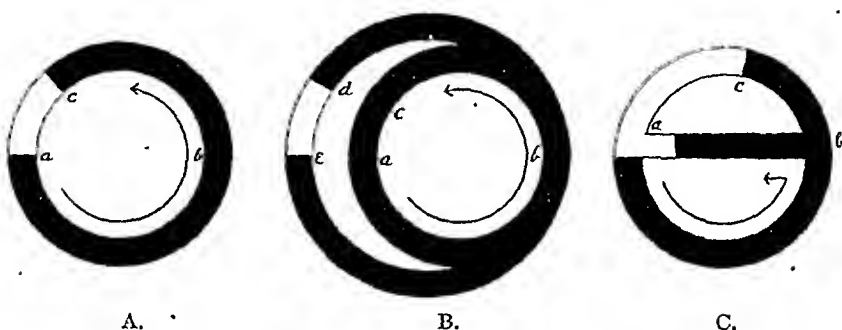


FIG. 1. A.—A diagram of a wave circulating in a ring of muscle. The wave travels in the direction *a, b, c*. *c* represents the crest of the wave and *a* represents its wake; these travel at the same rate and leave between them a constant gap of responsive muscle *ca*. The muscle which is refractory, *i. e.* in a state of contraction, is represented black. Suppose now that the refractory period suddenly lengthens; the muscle at *a* will remain refractory for a longer time and, as the crest *c* is all the time advancing, the gap *ca* will tend to close. If it closes, the circus movement on the original path (*abc*) will be brought to an end (Fig. 1 B); but the circus movement may itself continue if a new and longer channel (*d e*) is open to it (Fig. 1 B). Similarly if, while the conditions are those of Fig. 1 A and the refractory period suddenly shortens, the gap will increase in size. This increase in the length of the gap may open up a new channel (*b a* in Fig. 1 C) upon which the wave is now able to circulate.

a shorter channel. Variations in the length of the path are controlled by the dominant factors, refractory period and rate of conduction. It is to these two that we constantly return, from whichever standpoint we regard the wave. The length of path becomes a secondary consideration. A shorter circulation time, an increase in the number of circuit movements per minute is induced: (a) By an increased rate of conduction and (b) by a decrease in the refractory period when this permits the wave to accept a shorter path. Conversely a decrease in the number of circuit movements per minute is induced: (c) By a decreased rate of conduction and (d) by an increase in the refractory period when this forces the wave into a longer channel.

These are the broad effects, though the question is a complex

one. An increase or decrease in the rate of conduction will be mainly, perhaps solely, effective when the original gap is a material one. An increase or decrease in the refractory period will be mainly or solely effective, when the original gap is small and the wave is free, at the change, to take a shorter or longer channel.

The path may also change, theoretically, as a result of change in the rate of conduction. If this occurs, the effect of the secondary change would tend to neutralize the effect of the primary change, so far as an influence on rate of circulation is concerned. It is even conceivable that a decreased rate of conduction might lead, by materially shortening the path, to a decrease in circulation time (or an increase of the first to an increase of the second); but these paradoxical effects could only occur in very special circumstances. It is here to be remarked that probably in auricular muscle beating at a high rate, change in conduction and in the refractory period never occur apart from one another. Slow conduction appears always to be associated with lengthened refractory period; at all events this is so far as the variations described in the present lecture are concerned. These two changes, acting in concert, but in opposite directions so far as they influence the length of path, tend to neutralize each other.

*The Action of the Vagus.* Consider the action of the vagus, in the light of this theory of circuit movement: by reducing the transmission time it will expedite the circus movements; if, by reducing the refractory period, it reduces the length of path, the reaction will be in the same direction. Thus, vagal stimulation should accelerate the movements of the auricle in flutter and in fibrillation. It is well known to do so in experiment.<sup>9 12</sup> Clinically it is difficult to obtain a sufficiently powerful stimulation and, as a rule, little change of auricular rate is to be observed; thus, in recent attempts to alter the rate of the fluttering auricle by vagus pressure we have failed, neither can we detect the slightest change of rate in past records of this kind; in this connection it is interesting to observe that Levine and Frothingham<sup>5</sup> noted a slight change of rate in deep respiration, and the *relation* was the reverse of the normal; the increase of rate was seen during expiration, an act which exalts vagal tone. The direction in which they observed change is the direction which our theory would predict.

*The Action of Atropine.* The effects of atropine are the reverse of those of vagal stimulation. Thus in experiment, atropine increases the transmission intervals in the rapidly beating auricle;<sup>11</sup> it tends to prolong the refractory period.<sup>8</sup> Atropine, therefore, should slow the rate of auricular movement in the fibrillating auricle. This effect is actually witnessed in experiment.

The fall of rate where atropine is injected into patients who are the subjects of this disordered heart action is perhaps not absolutely constant, but usually the effect is definite and may be

conspicuous, in some cases it is very conspicuous, the auricular rate falling often 50, sometimes even 100 or 150 beats per minute (Fig. 2).

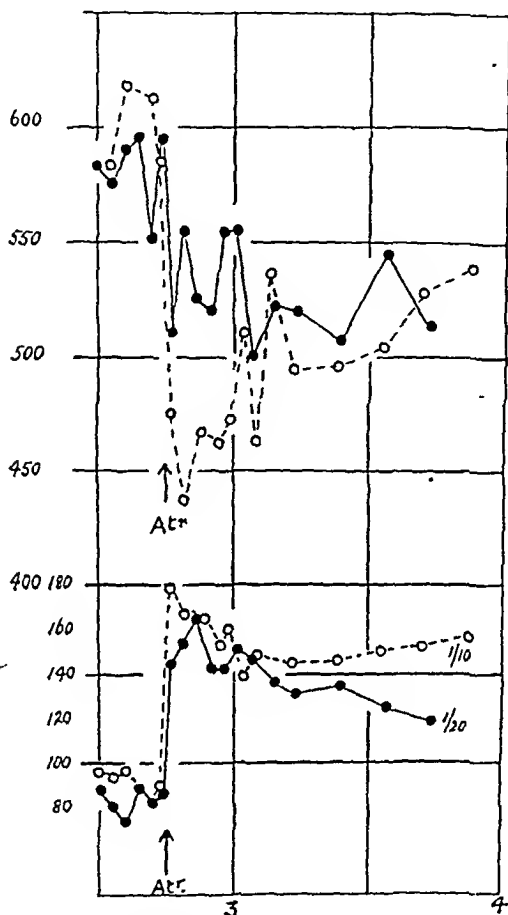


FIG. 2.—A chart from a case of fibrillation of the auricles, showing the effect of injecting  $\frac{1}{10}$  and  $\frac{1}{20}$  of a grain of atropine intravenously. The ventricular rate (lower curves) rises; the auricular rate (upper curves) falls. In these instances the falls of auricular rate are unusually conspicuous. Note that the reaction to  $\frac{1}{10}$  is greater than to  $\frac{1}{20}$  of a grain of atropine.

**The Action of Quinidine.** In considering the action of quinidine upon auricular fibrillation, we have to consider separately its action upon the auricle and its action upon the ventricle. These will be taken separately. Clinically two actions upon the auricle are witnessed, the first of which, namely, slowing of the auricular movements, is constant; the second of which, namely, restoration of the normal rhythm, is inconstant, occurring in about 50 per cent of our cases.

*Action of Quinidine in Slowing the Auricle.* When quinidine is given to dogs in similar doses per kilogram of body weight to those used therapeutically, among other reactions two stand out from our present point of view. Quinidine conspicuously lengthens the refractory period of the auricle; it lengthens this period 50 to 100 per cent. Its action in this respect is the most powerful known to be produced by therapeutic doses of any drug now used in cardiac maladies. The drug has a further action: it slows conduction in the auricular wall; the transmission intervals widen out; the increase is variable, but is usually from 50 to 100 per cent.<sup>11</sup>

Lengthened transmission intervals, according to the theory of circus movement, would profoundly slow the auricular rate. The longer refractory period of the muscle, if it exerted an influence upon rate, would act in the same direction; for if sufficiently prolonged it would divert the wave upon a longer path. Reflection will show that an equal percentage increase in refractory period and conduction time, would leave the wave in the same path, would leave the gap unaltered, but would double the time of its circulation and halve the number of circuits completed. Only when the effect on the refractory period outweighed that on conduction, would the path tend to lengthen. Thus, knowing the effects of quinidine upon auricular muscle, we are able to anticipate its influence on the rate at which the fibrillating auricle beats. It should produce, it does actually and invariably produce, profound slowing.

Thus, the effects of vagal stimulation, of atropine and of quinidine upon the rate of the fibrillating auricle, are clearly explained, if we accept as the basis of our argument, circus movement as the underlying cause of fibrillation.

*Restoration of the Normal Rhythm.* Theoretically, the normal rhythm can be restored in flutter or fibrillation, by closure of the gap between the crest and wake of the circulating wave, and by this means only; for the movement should continue so long as this gap of responsive muscle exists.

What factors will tend to close this gap so that it cannot reopen? The gap will shorten and tend to close if one of the following events happen alone:

1. An increased duration of the refractory period.
2. An increased rate of conduction.
3. A shortening of the path.

The last we need not consider, for actual and final closure would not occur so long as the longer original path remained open as an optional channel. Further, we need not consider an increase in the rate of conduction, for under quinidine, the reverse happens. Closure of the gap and the ending of circus movement would however receive an adequate explanation from lengthening of the refractory period. But fibrillation is not always terminated by

the administration of quinidine; it is not to be expected, since quinidine also slows conduction. The widened refractory period tends to close, the slowed conduction tends to open the gap; and it is only when the first effect exceeds the last that closure is to be anticipated. There is another reason why fibrillation should not always terminate under quinidine. Closure of the original gap may divert the circus movement along a longer path. A further increase in the refractory period might then prove effective, or it might not; the end result would depend on the extent of the longest available path.

It is evident that, knowing the effects of quinidine upon the muscle, and applying this knowledge to the theory of circus movement, we might anticipate the actual end results which are witnessed. Abrupt termination of the disorder in one case, failure to terminate in another.

Before leaving these effects of quinidine upon the auricular disorder, it is to be noted that quinidine does not act on the muscle alone; it also acts on the vagus. Its effect is to paralyze this nerve partly or completely. The manner of its action is not the same as that of atropine, for atropine acts on the nerve endings, while quinidine would appear to act, according to Dale's recent observations,<sup>1</sup> upon the nerve ganglia; the end result, so far as we are now concerned, is the same. Vagal tone decreases. Fortunately for our theoretical consideration, this change in nerve control acts in the same directions as do the direct effects on the muscle, a fact which is expressed correspondingly in the accompanying table.

TABLE.

	Refractory period.	Transmission time.	Rate of auricular movement.
Vagal stimulation . . . . .	—	—	+
Atropine . . . . .	+	+	—
Quinidine (direct action) . . . . .	+	+	}
Quinidine (indirect action) . . . . .	+	+	
			— .

Since both the direct and indirect action of quinidine are similar in end-results to those of atropine, it may be asked why the last drug is not capable of bringing fibrillation to an end. The reply is that in some circumstances it does do so; for the fibrillating auricle of the dog, atropine is usually an effective remedy,<sup>7 14</sup> stopping the disorder immediately. It is clear however that it is not effective clinically in chronic cases of fibrillation; though it might be so in more acute cases. A statement has been made that Hering<sup>3</sup> saw fibrillation abolished by atropine in man. This does not appear to have been so, the case being a disorderly rhythm of a different kind, as Hering<sup>4</sup> has stated. In patients, fibrillation is more firmly rooted than in dogs in which it has been produced by stimulation; and atropine, though it acts in the same directions as quinidine, has a far less powerful action.

It may be of interest to note that our observations upon atropine preceded our personal acquaintanceship with quinidine and its use in fibrillation.

*The effect of Quinidine on the ventricles* in fibrillation of the auricles is a complex one. In chronic fibrillation, a rise of ventricular rate is almost constant and is usually conspicuous. The rise coincides with the fall of auricular rate when single doses of the drug are given; using repeated doses, the ventricular rate often tends to fall away, although the auricular rate still remains low. Three factors appear to be involved, namely, the fall of auricular rate, loss of vagal tone and a direct action of quinidine on the conducting tissues. We may consider these separately.

When the auricle is beating rapidly and the ventricle is failing to respond to all the impulses so created, a fall of auricular rate tends to raise the rate of the ventricle. That is so because, as is well known, the degree of block becomes less as the auricular rate falls. In treating patients with quinidine this reaction is sometimes shown, unequivocally; thus sometimes, if the auricular rate is driven down to the neighborhood of 200 beats per minute, the ventricle, which previously responded to each second beat of the auricle, suddenly assumes the full auricular rate; there is an abrupt rise of ventricular rate to approximately double its former level. Such an abrupt rise can have but one meaning, it is a pure response to the events in the auricle. When, however, we deal with the more gradual rise in the earlier stages of administration, it is less easy to estimate accurately the part played by auricular rate, though we may be sure that this influence is exerted. Its degree is difficult to estimate because we must presume that vagal tone may also be changing.

To what extent are the vagi paralyzed by quinidine, given in therapeutic doses? If the action is comparable to that witnessed in experiment the paralysis should be considerable. Yet it can be shown that this is not the case, for if a single dose of quinidine is given, amounting to 0.6 or 0.8 gm., then an injection of atropine at the height of the quinidine reaction lifts the ventricular rate very appreciably (Fig. 3). Moreover, the rate, to which the ventricle can be forced by atropine alone, is a good deal higher than that which is attained under quinidine (Fig. 4), except in those cases in which the auricular rate falls so low that the ventricle attains the full auricular rate. The vagal paralysis produced clinically is at the most only partial. But the *number of beats* by which the ventricular rate rises, is greater when atropine is given alone than when atropine is given to a patient in whom the ventricular rate is already raised by quinidine (Fig. 4). This indicates that paresis of the vagus does play a part, though the degree in which this factor participates appears to be variable. An action upon the vagi as powerful as that seen in experiment is improbable,



since in the case of dogs the alkaloid is given intravenously and in man it is given by the mouth.

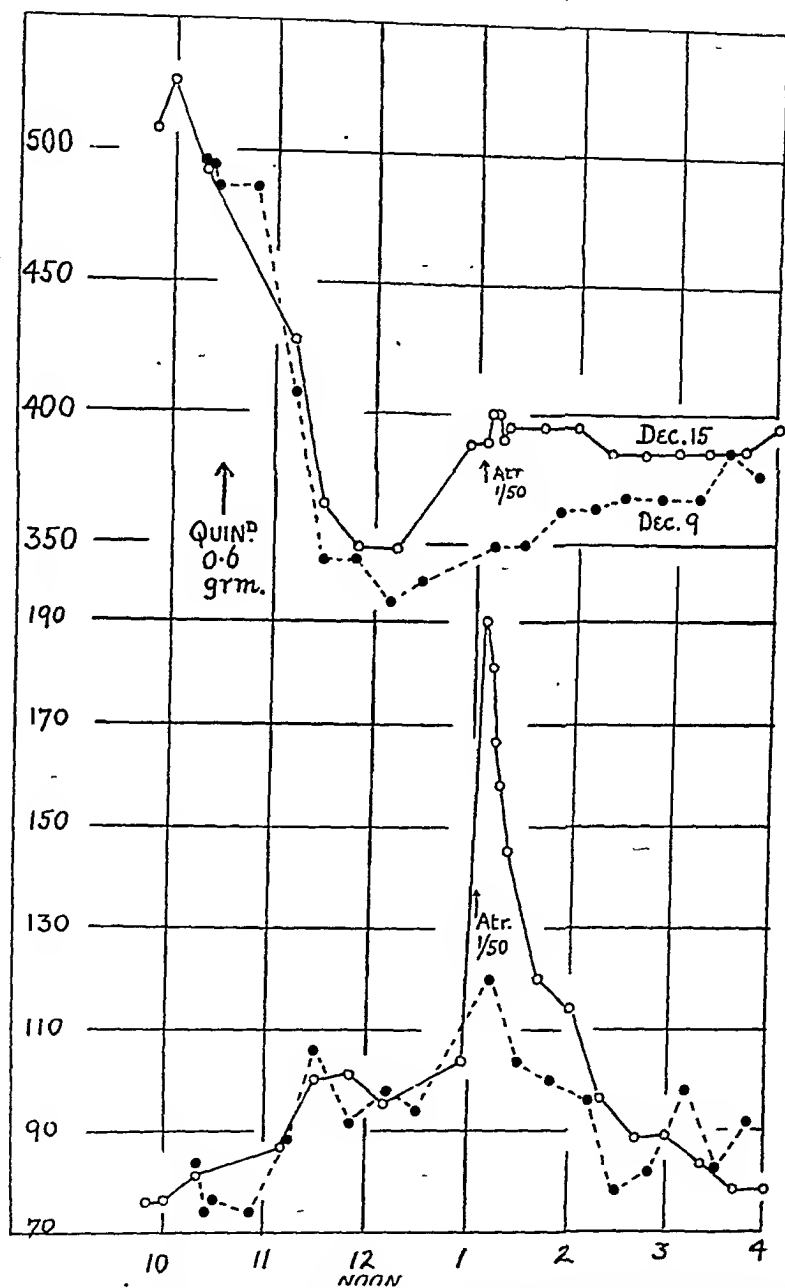


FIG. 3.—A chart from a case of auricular fibrillation, comparing the effect of a single dose of 0.6 gram of quinidine (black circles) with a similar dose of quinidine to which an intravenous dose of atropine has been added (plain circles). To show that the vagi are not paralyzed by the quinidine.

In experiments upon animals, almost all workers have noted that quinidine depresses conduction at the *A-V* junction. <sup>2 11 13</sup>

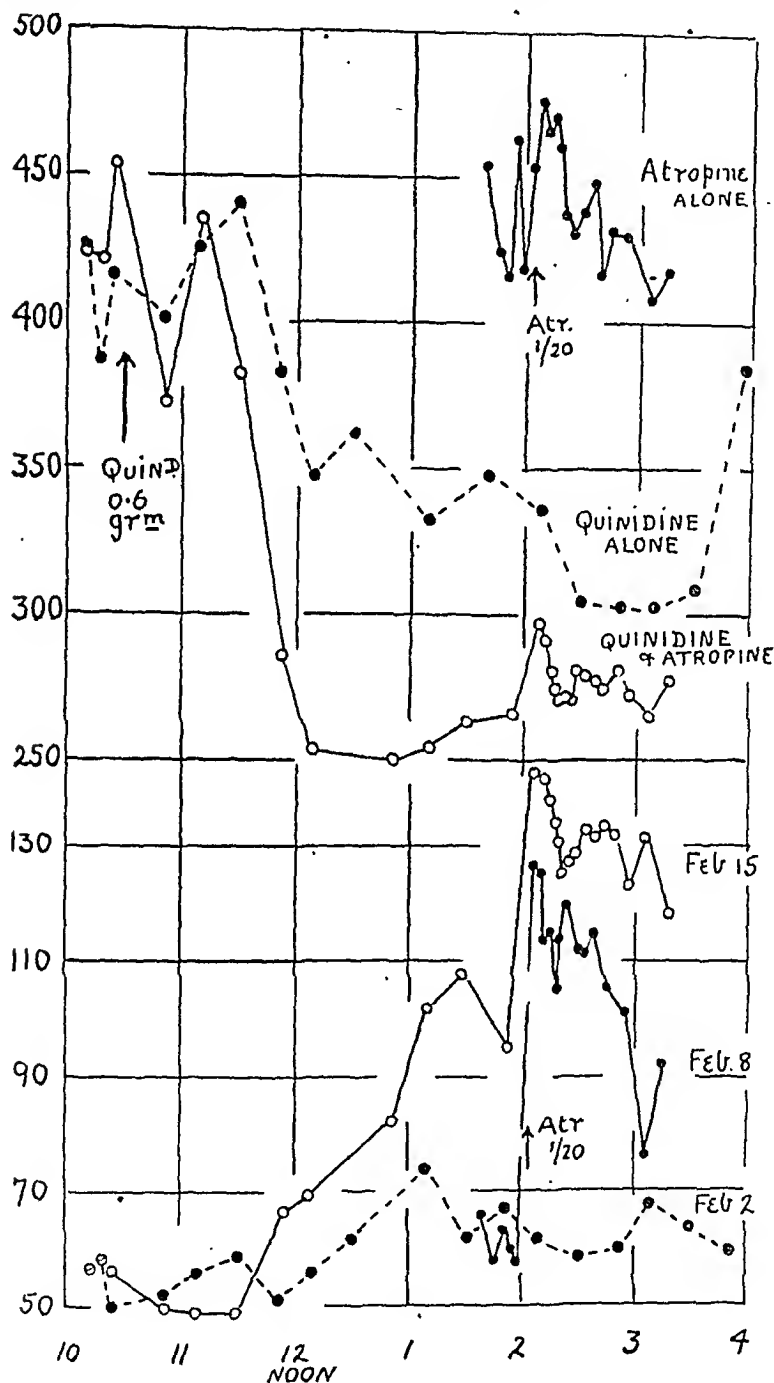


FIG. 4.—A chart from a case of auricular fibrillation, comparing the effect of (a) a single dose (0.6 gram) of quinidine (black circles, and broken line), of (b) a similar dose of quinidine to which an intravenous injection of atropine has been added (plain circles) and of (c) an injection of atropine alone (black circles and unbroken line).

This is more notable if the auricular rate is artificially maintained at a high level. It is due to a direct action on the muscle, for

atropine or vagal section does not affect it. Such an effect, if it exists in man, must influence the ventricle in the reverse direction to that so far discussed. Now this effect does exist in man, for in most instances where there is a sudden resumption of the normal rhythm the *P-R* interval is seen to be prolonged (Fig. 5); and this prolongation is clearly due to quinidine, for it disappears during the following twenty-four hours, if the administration of the drug is brought to an end. To what extent this controlling action upon the ventricle is exerted during the treatment of patients with quinidine it is not as yet possible to say; many more observations

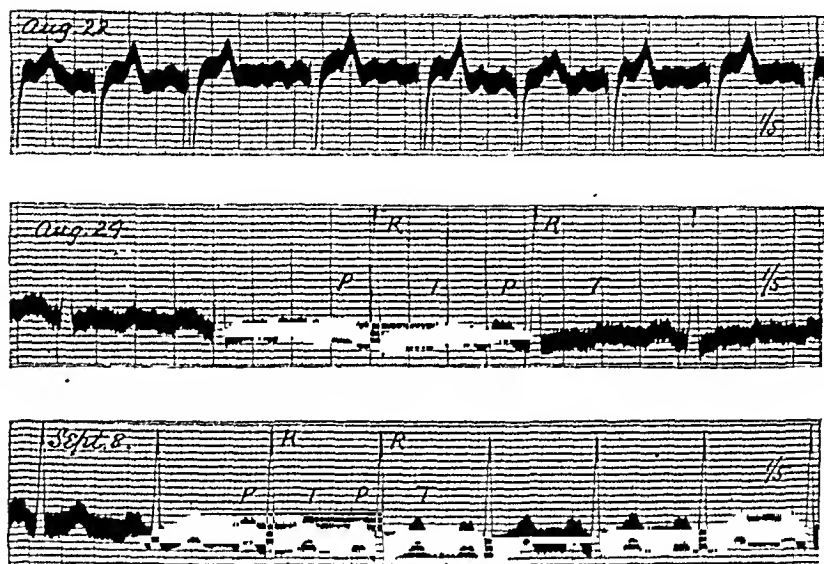


FIG. 5.—Three curves taken from a patient suffering from chronic fibrillation of the auricle. The first curve, which was taken by a direct lead from the chest wall, illustrates the fibrillation and was taken on the 22d of August. Quinidine was given amounting to 2.4 grams in two days. The normal rhythm became restored on the 24th of August. The second and third curves are from lead II and show this normal rhythm on the day of its restoration and a fortnight later. Immediately after its restoration the *P-R* interval is a little prolonged; the *T* wave is temporarily inverted.

are required before this question can be regarded as settled. The only indication of its influence during the administration of the alkaloid and while the auricles are still fibrillating is found in the tendency in many cases for the ventricular rate to fall when treatment is prolonged, a tendency otherwise unexplained. It would seem from this observation that the action comes into appreciable play only in the later stages of treatment, when the amount of quinidine in the body is at a maximum.

**The Theoretical Importance of Quinidine Reactions.** In my previous lecture I have indicated that I regard the reactions of clinical fibrillation to quinidine so far discovered as of more theoretical

than of practical importance. In the present lecture, I have tried to show that quinidine reactions, notable as they are, are to be explained if we assume that we are dealing with auricles in which circus movements have become established. The way in which observations and theory harmonize is, I think, sufficiently remarkable; this accord affords strong circumstantial evidence that the theory of circus movement is sound. The reactions of the heart to quinidine test a theory which, if true, is of fundamental consequence to our conceptions of disordered rhythm. They are severe tests; nevertheless, the theory still holds good. Let the final verdict in regard to the usefulness of quinidine in therapeutics be what it will, and the outlook is by no means unhopeful, the new knowledge gained from its reactions, the new lines of research which they have suggested and will continue to suggest, are far from negligible. Quinidine is not only testing new current theories,

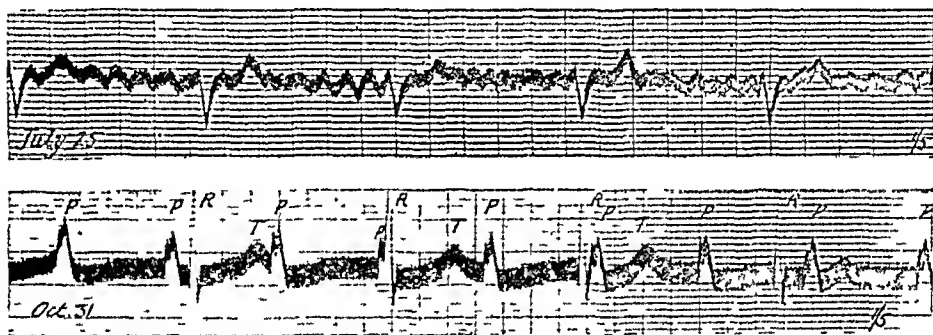


FIG. 6.—The upper is a curve taken on July 25 by leads from the chest wall. It shows fibrillation of the auricles and a slow and regular action of the ventricle. A single dose (0.6 of a gram) of hydroquinidine was given on October 31 and this restored the natural action of the auricle (lower curve). The mechanism is now one of complete heart-block; this continued unaltered.

but it is bringing valuable confirmation of older conclusions. One of the most striking of these is its final proof that fibrillation and flutter are fundamentally similar. Another incidental service which it is accomplishing, is that it is confirming the analysis of those cases of fibrillation in which the ventricle beats slowly. These cases have been interpreted as instances of combined fibrillation and heart-block; quinidine clearly displays this block when it restores the normal rhythm (Fig. 6). Recently we have treated a case of fibrillation in which the ventricle beat constantly and slowly at 30 to 40 per minute; when the auricle resumed its natural beat, complete block was disclosed. Quinidine will continue to bring knowledge of this kind; it is opening up many lines of original research.

If the theory of circus movement is finally accepted, careful research upon quinidine will continue to throw light upon the precise factors involved in the maintenance of this movement;

it has yet to guide us further in arriving at a clearer idea of the real distinction between the two closely allied conditions, fibrillation and flutter.

## REFERENCES.

1. Dale: Heart, 1921, 9, 87-89.
2. Hecht and Rothherger: Ztschr. f. d. ges. exper. Med., 1918, 7, 138.
3. Hering: Deutsch. Arch. f. klin. Med., 1908, 94, 185.
4. Hering: München. med. Wchnsehr., 1909, 56, 2483.
5. Levine and Frothingham: Archiv. Int. Med., 1916, 16, 818.
6. Lewis: Brit. Med. Jour., April 16 and 23, 1921.
7. Lewis and Cotton: Heart, 1921, 8, 37.
8. Lewis, Drury and Bulger: Heart, 1921, 8, 83.
9. Lewis, Drury and Bulger: Heart, 1921, 8, 141.
10. Lewis, Drury and Iliescu: Brit. Med. Jour., 1921, 2, 515.
11. Lewis, Drury, Iliescu and Wedd: Heart, 1921, 9, 55.
12. Rothherger and Winterberg: Archiv. f. d. ges. Physiol., 1914, 160, 42.
13. Schott: Deutsch. Archiv. f. klin. Med., 1920, 134, 208.
14. Winterberg: Archiv f. d. ges. Physiol., 1908, 122, 361; (see also Rothberger and Winterberg, *ibid.*, 1910, 131, 387).

---

## THE PHENOMENA OF RAYNAUD'S DISEASE.\*

By J. ARTHUR BUCHANAN, M.D.,

FELLOW IN MEDICINE, MAYO FOUNDATION, ROCHESTER, MINNESOTA.

IN 1862, Raynaud reported a series of cases of his own and collected from the literature another series of cases which "presented very unusual features on the part of the vascular apparatus." In 1874, Raynaud contributed a final article on the same subject, and following this, publications became voluminous in every country in the world. In the course of time stress was placed on phases of the phenomena which were not a necessary part of the picture, and some of the essential features were obscured. The phenomena are usually spoken of as "Raynaud's disease."

The symptoms manifested in Raynaud's disease are attributed to a disturbance of the vasomotor apparatus. Vasodilation was first observed by Claude Bernard, in 1851, following section of the cervical sympathetic nerve. He was so impressed by the heat of the rabbit's ear that he mistook the cervical sympathetic for a thermal nerve. This misconception was corrected by Brown-Séquard, who after sectioning the cervical sympathetic nerve stimulated the peripheral end. Constriction of the bloodvessels resulted. He interpreted this finding to mean that the cervical sympathetic nerve possessed primarily dilator and constrictor powers. In 1887, Heger demonstrated afferent vascular nerves which acted reflexly to produce dilation and constriction of the bloodvessels in general.

\* This work was done in the Section on Neurology, Mayo Clinic.

A controlling center for the vasomotor apparatus has long been considered a fundamental part of the mechanism, but the work of Porter and Hunt has shown that there are two centers, one related to the vascular dilator activities, the other being vasotonic or constrictor. The vasoconstrictor center has been located in the gray matter of the medulla with transfer centers in the gray matter of the spinal cord. The vasodilator center has not been located.

The response of vasomotor fibers to stimulation has been studied by Porter and Turner, Hunt, Gruber, Martin, Gunning and many others. The vasomotor center has been subjected to careful investigation, from the standpoint of pharmacology, by Pileher and Sollman. In all of the studies attention has been paid chiefly to the general effects of vasomotor stimulation or depression. The significance of these studies has been briefly summarized by Brown. As the local effects of a disturbance of the vasomotor apparatus are confined to constrictor and dilator manifestations with their concomitant signs, it is very difficult to reproduce in animals experimental phenomena similar to those observed in man. The most important experimental work has been carried out by Krogh, whose work has been recently reviewed by Policard. In man the local manifestations of a disturbance of the vasomotor apparatus are most apparent in the series of phenomena associated with the vascular apparatus, which are seen in Raynaud's disease. The local manifestations can be grouped under (1) changes in color and nutrition, (2) changes in sensation, (3) changes in the motor system, and (4) changes in the bones.

**Changes in Color and Nutrition.** These changes may be discussed under four main divisions, white, blue, red and black.

*White.* The term "local syncope" was introduced into medical literature by Raynaud to signify the sudden blanching of a part of the body. It is the primary stage of the phenomenon known as Raynaud's disease. It is the most frequent expression of a disturbance of the vasomotor mechanism and is entirely compatible with good health. It is rare, according to Osler, in any disease except in the syndrome described by Raynaud. Oppenheim has observed it, in addition to the Raynaud type of disease, in healthy neuropathic persons, in anemic persons or in persons with disease of the kidneys, and never accompanied by any further symptoms.

Local syncope expresses itself in a fairly characteristic manner. The affected part suddenly turns surprisingly white and cold. The part has the appearance of death. The color may be white with greenish tone, or with bright blue or bright red tinges. During the continuation of this phenomenon the temperature may be depressed, and often is, from  $15^{\circ}$  to  $20^{\circ}$ . The condition lasts for from a few minutes to a few hours. In the cases comprising this study the time varied from fifteen minutes to one hour. Osler has observed sweating of the part during the attack. If it

persists too long, gangrene may supervene. This phenomenon was well illustrated by Raynaud's first case. The patient, a woman, aged twenty-six years, had had symptoms in her fingers and toes since childhood. In moderately cold weather, and even in the height of summer, her fingers and toes became exsanguinated, completely insensible, and of a whitish-yellow color. The attacks came on without apparent cause and terminated by a period of painful reaction. She was always free from attacks during pregnancy. A very typical example of this manifestation was observed in the Mayo Clinic in the latter part of 1920. A married woman (Case 339485), aged fifty-two years, had had peculiar symptoms in her fingers and later also in her toes for the last twenty-three years. The trouble came on suddenly and continued without intermission. All the fingers of both hands to the metacarpophalangeal knuckles suddenly turned white with a clear line of demarcation. The pallor was associated with a tingling sensation. The attack was always brought on by cold, such as dipping the hands in cold water, going from a warm room into a cold room or going out of the house into the outside air during cool weather. The attack lasted for from fifteen minutes to two and one-half hours. Otherwise her health was good. The patient's son had the same difficulty.

*Blue.* In order to distinguish the periodic attacks of blueness in various parts of the body, Boyer introduced into medical literature the term "local asphyxia." Raynaud applied this term to the second stage of the phenomena observed by himself. The blueness, characteristic of local asphyxia, may be bluish white or violet-gray, or there may be redness with varying degrees of blueness. The blueness disappears on pressure, with an abnormally long interval before the return of normal or of the bluish coloration. There may be marbling of the affected part, consisting of blue rings with pale centers. There is a slight diminution of the local temperature, but much less than that observed during local syncope. There are frequent sudden changes of color. Often the affected part swells temporarily or sweats, making the part cold and clammy. If the local asphyxia persists, as it may, for years, a sort of false edema results, owing to the excessive predominance of cellulo-adipose tissue brought about by undernutrition. This phase of the phenomena of Raynaud's disease is the most inconveniencing, as it renders life miserable to the patient because of the pain which is so commonly associated with it. Local asphyxia and local syncope may succeed one another rapidly, and may appear as constantly interchanging processes; local asphyxia is usually of longer duration than local syncope. Solis-Cohen spoke of these rapid changes as vasomotor ataxia. Gangrene is produced by too long persistence of local asphyxia. Local asphyxia, like local syncope, is paroxysmal, and recurrent, and may be symmetric or asymmetric. It is

more painful than syncope. Often the epidermis desquamates after an attack. In some cases the symptoms occur regularly at a certain hour, and with each new attack the severity of the cycle increases. The attacks finally disappear by a gradual daily decline of severity of symptoms.

The usual course of local asphyxia was typified in a patient (Case 231824), who visited the Clinic in 1918 on account of a peculiar trouble in the legs. One and one-half years before she suddenly developed cyanosis and very slight edema in the left leg. The cyanosis came on when she was exposed to cold or when she was walking. Six months later she developed similar trouble in the right leg, and still more recently her hands became involved. During the attacks menstruation was suppressed, often as long as two months; when the attacks subsided it was established. Her finger nails and one great toe nail dropped off without any apparent cause. November 15, 1920, she was improved, but still having trouble, especially when walking.

In Raynaud's series of cases under the heading of local asphyxia a patient was described who, when exposed to the cold, had marked cyanosis of the nose, chin, cheeks, hands and feet. The phenomena were first a paling, then a violet or slaty-white tint and later a deep purple. The discoloration faded quickly with warm applications.

In 1883, Cavaufy described a condition of symmetric congestive mottling which is probably a universal distribution of a mild form of local asphyxia. In this condition the mottlings or marblings were particularly marked. A similar case was observed in a young man in the Mayo Clinic in the early part of 1920, in whom the mottlings were generally distributed and the skin was cold and clammy. After the most painstaking general physical and neurological examination no organic lesion capable of producing the condition could be demonstrated.

*Red.* This coloration of the skin is designated by the term "local hyperemia." It was not observed by Raynaud and occurs only infrequently. It may follow either local syncope or asphyxia. It has never been observed alone, unless the simple, burning, tingling, recurrent redness of one or the other external ear so commonly experienced by everyone, and about which there are many superstitions, belongs to this category, and is a common and distinctive demonstration of some vasomotor disturbance which is not associated with any other signs. During the stage of local hyperemia the part is bright red, usually with palpably increased arterial pulsations, increased warmth of the part, slight increase in moisture of the part and at times an unpleasant sensation, almost approaching pain, which is, however, usually described as tingling.

*Black.* The presence of a blackish discoloration of parts of the body has been designated by various titles such as spontaneous gangrene, idiopathic gangrene and symmetric gangrene, and it is



to this phase of the events described by Raynaud that most importance has been attached. The words symmetric and gangrene have received undue emphasis. In the type of cases originally described by Raynaud if gangrene is lacking or if it is present but does not happen to be symmetric, the case is usually spoken of as "not typical," "not Raynaud's disease," and a diagnosis is not made. The history of the case is classified under some hit-or-miss term, so that it eventually becomes lost for all purposes of study. The gangrene usually affects the peripheral parts, and is of a dry type, with clear demarcation from the normal tissues. The part may continue in a black, dry state for months before finally sloughing. In the language of Raynaud, there is a tendency for the gangrene to be symmetric. It may come on spontaneously, either without syncope or asphyxia, or follow one or both. The parts affected by gangrene heal with a peculiar tapering deformity which is quite striking. The gangrene may appear as a slight ulceration, which heals with a small white scar, or the part may become dry, with thickening of the skin, which is characterized by a brown, scaly desquamation. The gangrene may be massive and involve a finger, a forearm, a leg or even a leg with a portion of the thigh.

**Changes in Sensation.** Raynaud stated that pain is almost a constant finding; it may be sharp and paroxysmal, coinciding with manifestations of syncopal and cyanotic attacks, or a painful numbness followed by a sensation of burning and shooting. It is not limited to the affected extremities but radiates to every limb. The pain is increased by pressure; it is usually the first symptom to attract attention. Osler observed that pain commenced with the onset of local asphyxia, and he also observed considerable pain in cases in which the stage of gangrene had been reached. The pain may be present in one attack and absent in another. Cassirer observed pain, usually burning, in most cases. He called attention to the lack of either peripheral or spinal distribution.

Analgesia occurs rarely, but infrequently there is a slight diminution of tactile sensation. Heat and cold sensations are not changed. There may be no unusual sensations on returning to normal color after an attack of syncope or asphyxia, or there may be burning, tingling, pricking or a combination of peculiar sensations.

The severity of the pain is illustrated in one of the patients in the Mayo Clinic series who for thirty years had been troubled with attacks of syncope and asphyxia and intense pain in both feet. Cold weather increased the symptoms, but they were present to some extent in all seasons. Treatment did not avail, and each succeeding year the pain became more intense until the patient finally died from what, for want of a better term, was designated "physical exhaustion."

**Changes in the Motor System.** Motor disturbances such as clumsiness and slowness in performing the ordinary work are commonly present. Barlow has noticed that patients complain chiefly of difficulty in accomplishing small movements.

**Changes in the Bones.** Cassirer was the first to observe changes in the bones in association with the phenomena of Raynaud. He described the changes as atrophic, a thinning

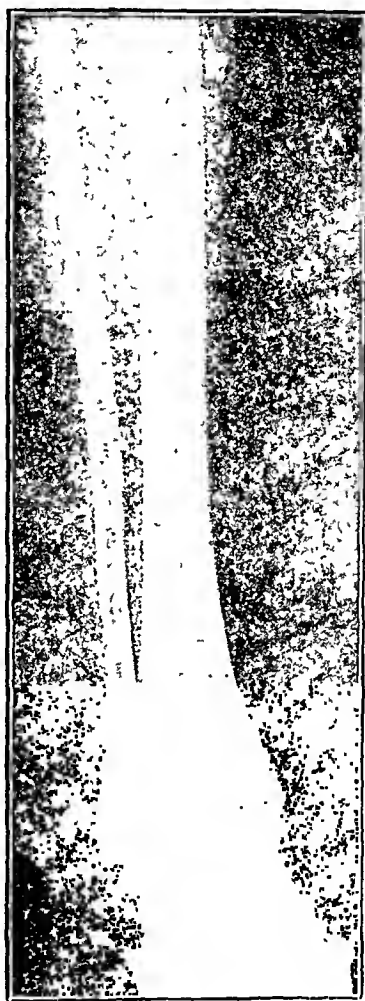


FIG. 1 (Case 231824).—Thinning of the bony cortex, widening of the marrow space and sharpening of the canalicular systems.

of the cortex of the bone with consequent increase of the marrow space and sharpening of the outline of the canalicular systems. The bone may be completely absorbed without becoming necrotic or forming a sinus. Oppenheim has made similar observations. An atrophic process in both bones of the right leg was observed in a patient in the Mayo Clinic (Case 231824). The changes are clearly shown in Figure 1.

The histories of 67 patients observed in the Mayo Clinic were studied; 50 of these were traced.

TABLE I.—INCIDENCE OF RAYNAUD'S DISEASE IN RELATION TO THE TOTAL REGISTRATIONS OF PATIENTS IN THE MAYO CLINIC EACH YEAR.

Year.	Patients.	Percentage of registrations.
1911	4	0.026
1912	2	0.013
1913	3	0.012
1914	5	0.016
1915	5	0.014
1916	10	0.023
1917	7	0.014
1918	13	0.026
1919	9	0.014
1920	9	0.015

The patients came from twenty-two of the states in the United States and from three provinces in Canada. With the exception of 1 born in Austria, 1 in Italy, 1 in Switzerland and 1 in Holland, all were born in North America. The birthplace, and places of residence are so diversified that they can have no weight as etiological factors.

TABLE II.—40 (59.8 PER CENT) FEMALES AND 27 (40.2 PER CENT) MALES.

Age.	Patients.
Under 10 . . . . .	1
11 to 20 . . . . .	6
21 to 30 . . . . .	20
31 to 40 . . . . .	16
41 to 50 . . . . .	15
51 to 60 . . . . .	7
61 to 70 . . . . .	1
71 to 80 . . . . .	1

Twenty-one definite occupations were represented other than that of housewife. It was not demonstrated that physical and nervous strain incident to any one type of occupation or social stratum was a cause of the condition.

TABLE III.—STATE OF HEALTH (NOVEMBER 15, 1920) OF THE 50 PATIENTS TRACED.

	Patients.
Improved . . . . .	12
General health good . . . . .	13
Entirely well . . . . .	2
No change . . . . .	9
Worse . . . . .	8
Died:	
Tuberculosis . . . . .	1
"Exhaustion" incident to intense pain . . . . .	1
Influenza . . . . .	3

The results shown in Table III do not give the usually gloomy outlook for such patients.

TABLE IV.—DURATION OF DISEASE.

	Patients.
5 years or less . . . . .	37
10 years or less . . . . .	15
15 years or less . . . . .	5
20 years or less . . . . .	4
25 years or less . . . . .	3
30 years or less . . . . .	1
35 years or less . . . . .	0
40 years or less . . . . .	1
45 years or less . . . . .	1

It may be definitely stated that a patient may have Raynaud's disease for many years, with more or less good general health. This was illustrated in a patient, aged forty-eight years (Case 305726), who visited the Mayo Clinic in 1920 on account of painful ulcerated areas in her feet. When she was five years of age she began to be troubled with purple spots on her legs which appeared at varying intervals. This kept up until she was twenty-six years of age, when small ulcers appeared on both legs following an attack of blue spots. These ulcers lasted a short time, healed and again appeared. The patient was always well during her pregnancies, and for one period of three years had no trouble. This period represents what may happen when it is believed the condition is cured by some line of treatment. Following this interval blue spots, and at times extreme pallor of the right leg, appeared. In a short time the trouble appeared in the left leg and then in both forearms. There was frequent desquamation of the epidermis of the legs. Shortly before she came to the Clinic, her left great toe became black and intensely painful. Still more recently small ulcers appeared on the left small toes, then on the left third toe and finally on the left great toe. This all took place during the course of three weeks. There had been an ulcer on the right leg more or less constantly for seven years. The patient's general health had been good.

**Mode of Onset.** Sixty (89.5 per cent) of the patients described the mode of onset as very sudden. Two patients did not describe it and 5 described it as very gradual. "Sudden onset" means that at some particular hour when the patient was in good health a portion of the body suddenly turned white, blue or black. "Gradual onset" means that tingling, numbness, clumsiness or an indescribable discomfort was experienced in attacks, followed at a later period by the color phenomena. In 1 instance the condition followed immediately an attack of diphtheria, in 1 an attack of unexplained jaundice and in 1 it became aggravated after an attack of influenza. This patient was having some vascular disturbance in the fingers. In the other cases it was impossible to find a condition which might be regarded as a causal factor. There was nothing in the histories of

the patients to indicate that the disturbances depended on a toxic process.

TABLE V.—PATIENTS WITH COLOR CHANGES.

	Patients.
Syncope alone . . . . .	9
Asphyxia alone . . . . .	6
Gangrene alone . . . . .	1
Syncope and asphyxia . . . . .	28
Syncope without gangrene . . . . .	0
Asphyxia and gangrene . . . . .	13
Syncope, asphyxia and gangrene . . . . .	11

The syncopal and asphyxial attacks lasted, as a rule, for from fifteen minutes to one hour. The asphyxial attacks, in 1 case, were continuous for four months before the onset of gangrene. The gangrene lasted usually about two months before sloughing of the part occurred. Local hyperemia with the other vasomotor phenomena of Raynaud's disease was found in 8 (11.94 per cent) patients in this study. The occurrence of this discoloration was clearly shown in a woman, aged forty-one years (Case 331049), who visited the Clinic in 1920 after having suffered for three years with attacks in which the fingers to the metacarpophalangeal joints of both hands, when exposed to cold, became dead white, then purple and in a short time red, then gradually regained their normal color.

TABLE VI.—SENSORY NERVOUS SYSTEM SYMPTOMS.

	Patients.
Intense pain . . . . .	17
Slight pain . . . . .	9
Numbness . . . . .	20
Tingling . . . . .	11
Pricking . . . . .	1
Itching . . . . .	1
Burning . . . . .	9
Soreness . . . . .	4

One patient had lost tactile sensation over the dorsal and palmar surfaces of the hands and another patient had anesthesia of both little fingers.

Patients who were troubled with syncopal and asphyxial attacks of the fingers usually experienced clumsiness during the period of the attacks. One patient limped intermittently while he was having syncopal attacks in his legs, which were affected alternately. A similar case was described by Westphal. Motor disturbances were not a common finding.

The lesions were bilateral and symmetric in 38 (56.7 per cent) patients and asymmetric in 29 (43.2 per cent). The tendency to symmetry and the slowly healing gangrenous process are shown in a girl, aged five years (Case 282988), who was brought to the Clinic in 1919 on account of deformities of the lips following a gangrenous process. When she was fifteen months old, purple-red spots appeared

suddenly over the entire body, in the course of which the first two phalanges of the first and second fingers of the right hand turned red, then black, and finally sloughed off. The trouble occurred

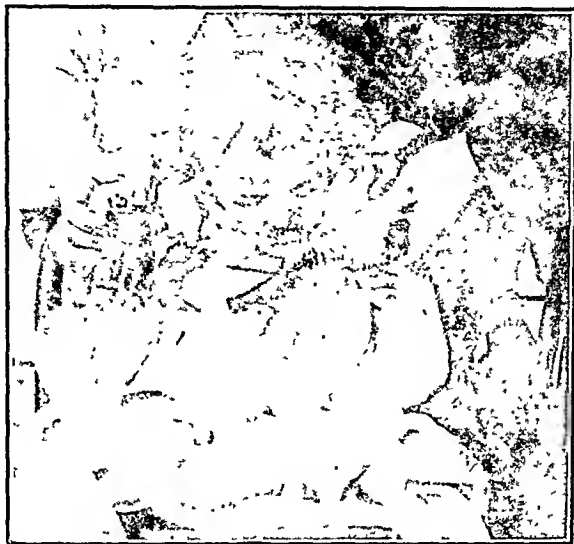


FIG. 2 (Case 282988).—Peripheral and symmetric tendency of the lesions with the terminal sloughing in the right forearm. The left forearm shows the atrophic type of gangrene and the gradual sloughing process. The lip margins are in an advanced state of gangrene. The state of nutrition is fairly good, as shown by the fulness of the cheeks. (Courtesy of Dr. Gordon B. New.)



FIG. 3 (Case 282988).—Later stage of patient shown in Fig. 2. Type of scar, deformities and the excellent state of nutrition in the presence of serious feeding difficulties.

during the winter months. One year later she had another attack with small sloughs over the legs; these healed with whitish scar formation. The lower third of both forearms turned black, became gangrenous and then sloughed, and healed with the type of deformity shown in Figures 2 and 3. During this attack the lip margins sloughed off. The child suffered intensely from pain during the process. Since November 15, 1920, she has had syncopal attacks of various parts of the body. This case is similar to a case reported by Raynaud. The patient, a woman, aged twenty years, presented herself at the Academy of Sciences, Paris, bringing her forearms in her coat pockets. They were black and dry like the hands of a little mummy. When she was seven years of age, following a slight fever, a withering process developed in both forearms, which finally sloughed, leaving the two stumps, which she used to draw the unusual relies from her pockets.

TABLE VII.—DISTRIBUTION OF SPONTANEOUS AMPUTATIONS THE RESULT OF GANGRENE.

	Patients.
Little toes . . . . .	5
Fingers . . . . .	6
Great toe . . . . .	2
Both forearms and lips . . . . .	1
Right femur . . . . .	1

TABLE VIII.—DISTRIBUTION OF SMALL GANGRENOUS AREAS.

	Patients.
Entire body . . . . .	19
Fingers . . . . .	5
Left side of face . . . . .	1
All of face . . . . .	2
Knee . . . . .	1
Side of tongue . . . . .	1
Back of throat . . . . .	1

The universal distribution of the scar formation following gangrenous processes is shown in Figures 4 and 5, photographs of a man, aged eighteen years, (Case 144087), who visited the Clinic in 1915 on account of multiple gangrenous areas over the extremities and the trunk. One year before, he had had a sudden attack of cyanosis of the forefinger of the right hand, which continued for four months; the finger then turned black and gangrenous. The tip of the finger finally sloughed and the process spread up the finger. Early in the condition the right ring finger and little finger became cyanotic. Three weeks after the primary onset the third, fourth and fifth fingers of the left hand became cyanotic, and this continued off and on for eight months, when gangrene developed in the left hand. Later his knees, the side of his tongue and many small areas over the body became cyanotic. These areas finally became gangrenous, sloughed and healed, with small white scar formation. At the time



FIG. 4 (Case 144087).—Minute scars which represent the results of previous gangrenous areas. The patient was markedly emaciated.



FIG. 5 (Case 144087) —Tendency to symmetric distribution of the gangrene. Multiple scar formation on the forearms.



of his visit to the Clinic the condition was widespread, and he was in a state of marked physical exhaustion. The pain was increasingly severe with each new attack. November 15, 1920, he was still alive but little improved, except for the disappearance of the pain. The syncopal attacks in the fingers had not been marked, and they continue. They are usually followed by asphyxial attacks.

**Blood-pressure.** The systolic blood-pressure was within normal limits in 49 (73.1 per cent) patients, above normal in 11 (16.4 per cent) and below normal in 7 (10.4 per cent). The diastolic blood-pressure was within normal limits in 14 (20.8 per cent) patients, above normal in 33 (49.2 per cent) and below normal in 12 (17.8 per cent).

TABLE IX.—EVIDENCE OF NO RELATIONSHIP BETWEEN PHENOMENA OF RAYNAUD AND PULSE-PRESSURE.

Pulse-pressure, mm. Hg.	Patients.
10 to 20 . . . . .	1
21 to 30 . . . . .	5
31 to 40 . . . . .	24
41 to 50 . . . . .	16
51 to 60 . . . . .	6
61 to 70 . . . . .	4
71 to 80 . . . . .	1
91 to 100 . . . . .	1
100 to 110 . . . . .	1
Not recorded . . . . .	8

The absence of a fixity of blood-pressure variations in a vasomotor disturbance coincides with the experimental work of Krogh.

**Blood Picture.** The hemoglobin was recorded in 45 (61.1 per cent) patients. The percentage ranged from 47 to 88, with an average of 81. The erythrocytes were counted in 34 patients, and ranged from 2,820,000 to 5,890,000 per cmm., with an average of 4,810,000 per cmm. The leukocytes were counted in 34 (50.7 per cent) patients, and the lowest count was 5600 cells per cmm.; the highest was 13,400 cells per cmm., with an average of 7800 cells per cmm. A differential count was made in 12 patients. The average type of cell found was: polymorphonuclears, 63.1 per cent; eosinophils, 4.5 per cent; small lymphocytes, 23.9 per cent; large lymphocytes, 4.5 per cent; and basophils, 1.4 per cent. One patient had a marked secondary anemia.

**Pulse-rate.** The pulse-rate was normal in 12 patients, increased in frequency in 4 and lessened in frequency in 26; it was not recorded in 25.

**Urine.** The examination of the urine was negative in all cases. Hemoglobinuria was not observed in any case.

TABLE X.—RELATION OF SEASON AND EMOTION TO ATTACKS.

	Patients.
Cold . . . . .	31
Cold and emotion throughout the year . . . . .	2
Emotion . . . . .	5
Cold of winter months . . . . .	7
Cold of autumn months . . . . .	1
No apparent exciting factor but attacks throughout year . . . . .	20
No apparent exciting factor; attacks limited to summer months . . . . .	1

To the patients who had symptoms throughout the year, the search for fixed temperatures became an obsession. One of the patients was financially able to afford to change her location every few months; in this manner she had passed through several years without trouble. She was subject to local syncope and asphyxia, the most troublesome type from the standpoint of actual suffering.

**Incidental Findings.** One patient was always well during her pregnancies. Menstruation was suppressed in 1 patient during the period of attacks; 1 had excessive menstruation; 1 had irregular menstruation; and 1 had transient attacks of hemiplegia during the attacks. One man was sexually impotent during the attacks. The patients observed that if they pricked their fingers during the stage of local syncope no bleeding occurred. One patient had eighteen convulsions during the two years that she had been suffering from Raynaud's phenomena. This patient was also subject to migraine, so that it is debatable whether her convulsions were owing to vasomotor changes of the new condition or whether they were the expression of the migraine-epilepsy syndrome.

**Associated Conditions.** One patient had asthma; 1 had duodenal ulcer; 3 patients had migraine; 1 patient had angioneurotic edema; 1 patient had pulmonary tuberculosis; and 1 patient had hysteria. Pathological changes extensive enough to justify the belief that they had any relation to the vasomotor phenomena were not observed. All the patients had negative Wassermann reactions on the blood and histories negative for syphilis.

**Measures for Relief.** The attacks were relieved by warmth in 5 patients; by cold applications in 1 patient; and 1 patient was relieved by taking Bland's pills. Bier's hyperemia was tried in all the early cases, but no benefit was obtained. No patient was relieved by elevation of the affected part. A warm, non-variable climate seemed to be the only factor to afford relief. Some of the patients were able to lessen their attacks by wearing woollens and protecting themselves from the cold as much as possible. Thyroid extract produced no definite benefit. The eradication of foci of infection was without results.

**Discussion.** The basic mechanism involved in the production of the symptoms manifested in Raynaud's disease remains obscure, but the phenomena observed coincide satisfactorily with the theoretic and experimental possibilities of a disturbance of the vasomotor appar-

atus. The attacks of syncope are no doubt constrictor, as the part or parts are partially or completely bloodless during the attacks. This is shown by the absence of hemorrhage on pin prick, and further by the total lack of color of the part and the lowered temperature. The asphyxial attacks are probably also constrictor and not dilator, as is commonly believed. The cyanosis may be the result of a slowing of the passage of blood through the peripheral vasculature with its consequent prolonged retention in the parts; this is due to the increased resistance with which it meets on account of the partially or in places completely constricted lumina of the finer bloodvessels. That the local asphyxia is constrictor, but to a less extent than that observed in syncope, is further substantiated by the lessened degree of lowered temperature. Any explanation which fails to consider the constriction as involving arterioles, capillaries and venules is unsatisfactory. A limited constriction of the arterioles and capillaries would result in a swelling of the tissues above the site of constriction and a cyanosis beyond the point of constriction. This is not observed in the phenomena of Raynaud. A constriction of the venules would result in a swelling in the regions to the proximal side of the constriction. This is not observed. The condition must involve all three of the finer ramifications of the vascular system in order to produce the ordinary consequences of the condition. The hyperemia is dilator, as evidenced by the color, the increase of temperature of the part and the palpable pulsations of the finer peripheral vessels.

The search for a tangible causative factor has been without results. It is not possible to attribute the condition to toxemia, as no possible toxic cause is visible. The infrequency of acute infections in the onset minimizes the importance of the ordinary type of infections as etiological factors. Heredity plays no part. Whatever may be the causal agent the method of its action seems in most cases peripheral on the vasomotor nerves rather than on the central mechanism, although it is possible that in certain cases both may be affected.

The name for the disease has always been indefinite. For a better understanding of the particular phase of the disease discussed the term "Raynaud's disease" should be discarded and in its place "local syncope of Raynaud," or "local asphyxia of Raynaud," or "gangrene of Raynaud" substituted. Various combinations of these terms can be used so that the phase of the condition under discussion may be easily understood. When all three phases of the condition are present the term "phenomena of Raynaud" would be a satisfactory substitute.

#### BIBLIOGRAPHY.

1. Barlow, T.: Raynaud's disease, in *System of Medicine*, Allbutt, C., and Rolleston, H. D. London, Macmillan & Co., 1910, 7, 120-149.

2. Bernard, C.: *Experience sur les fonctions de la portion céphalique du grand sympathique*. *Compt. rend. soc. de biol.*, 1852, 4, 155.
3. Boyer, A.: Quoted by Raynaud.
4. Brown, W. L.: *The Sympathetic Nervous System in Disease*. London, H. Frowde, 1920, 114-116.
5. Brown-Séquard, C. E.: *Sur les résultats de la section et de la galvanisation du nerf grand sympathétique au cou*. Paris, E. Thunot, 1854, 9 pp.
6. Cassirer, R.: *Die vasomotorisch tropischen Neurosen*. Berlin, S. Karger, 1901, 609 pp.
7. Cassirer, R.: *Handbuch der Neurologie*. Berlin, Springer, 1914, 4, 185, 203.
8. Cavafy, J.: *Symmetrical Congestive Mottling of the Skin*. *Trans. Clin. Soc. London*, 1883, 16, 43-48.
9. Gruber, C. M.: *The Response of the Vasomotor Mechanism to Different Rates of Stimuli*. *Am. Jour. Physiol.*, 1917, 42, 214-227.
10. Gunning, R. E. L.: *Comparative Vasomotor Reactions in Branches of the Arterial Tree*. *Am. Jour. Physiol.*, 1916, 41, 1-4.
11. Heger: Quoted by L. Luciani, *Human Physiology*. London, Macmillan & Co., 1911, 1, p. 355.
12. Krogh: Quoted by Policard.
13. Martin, E. G., and Mendenhall, W. L.: *The Response of the Vasodilator Mechanism to Weak, Intermediate, and Strong Sensory Stimulation*. *Am. Jour. Physiol.*, 1915, 38, 98-107.
14. Oppenheim, H.: *Lehrbuch der Nervenkrankheiten*. Berlin, S. Karger, 1913, 1941 pp.
15. Osler, W.: *Vasomotor and Trophic Disorders*, in *Modern Medicine*, Osler and McCrae. Philadelphia, Lea & Febiger, 1915, 4, 975-997.
16. Pileher, J. D., and Sollman, T.: *Studies on the Vasomotor Center*. *Jour. Pharmacol. and Exper. Therap.*, 1914-1915, 4, 323-411.
17. Policard, A.: *Les phénomènes de motricité capillaire*. *Lyon chir.*, 1921, 18, 51-68.
18. Porter, W. T.: *The Vasotonic and Vasoreflex Center*. *Am. Jour. Physiol.*, 1915, 36, 418-422.
19. Raynaud, M.: *De l'asphyxie locale et de la gangrène symétrique des extrémités*. Paris, Rignoux, 1862, 177 pp.
20. Raynaud, M.: *Nouvelles recherches sur la nature et le traitement de l'asphyxie locale des extrémités*. *Arch. gén. de méd.*, 1874, 153, 5-21.
21. Solis-Cohen, S.: *Vasomotor Ataxia: A Contribution to the Subject of Idiosyncrasies*. *Am. Jour. Med. Sc.*, 1894, 107, 130-147.
22. Westphal, A.: *Ueber hysterische Pseudotetanie mit eigenartigen vasomotorischen Störungen*. *Berl. klin. Wchnschr.*, 1907, 44, 1567-1570.

## THE SPLEEN AND DIGESTION.

### STUDY II. THE SPLEEN AND PANCREATIC SECRETION

BY WILLIAM DEP. INLOW, M.S., M.D.,

FELLOW IN SURGERY, DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY, THE  
MAYO FOUNDATION, ROCHESTER, MINNESOTA.

(Presented for publication July 1, 1921.)

THE theory of a functional relationship between the spleen and the pancreas has received much study. Especially in continental Europe in the closing years of the nineteenth century and the first few years of the twentieth century publications of experimental researches in the various languages by numerous investigators were

frequent, and discussions at meetings of physiologists were rife. This turmoil was largely owing to the continual stirring up which the scientific world received at the hands of Herzen, at Lausanne, who, though he found this world largely skeptic of his tenets, nevertheless persisted throughout the major portion of his life in battling persistently for his beliefs.

**Review of the Literature.** The idea that the spleen in some way influences the pancreas is apparently modern, and does not date as far back in medical antiquity as does the assumption of a similar relationship between the spleen and the stomach. Yet even in the seventeenth century a possible function of the spleen in pancreatic digestion had been suggested. This doctrine was reviewed by Daniel Duncan, of the famous faculty of Montpellier, in 1683: "L'acide fixé du suc pancréatique et le voisinage du pancréas et de la rate, pourroient bien faire croire à quelqu'un que cette glande est l'émonctoire de ce viscère; et que comme le sang de la veine porte va passer par le foye pour quitter les soufres dont il est chargé, ainsi, le sang de la veine splénique se va de charger dans le pancréas de ce suc aigre qu'il a pris dans la rate." Duncan did not subscribe entirely to the view thus expressed. He had never seen the canal between the two organs which some anatomists of his epoch had pretended to have found, and he believed the route from the spleen to the pancreas was more circuitous. He believed the product of the spleen to be poured into the torrent of the general circulation and then brought to the pancreas through a branch of the celiac artery. How similar to the modern conception of internal secretion this is!

The eminent physiologist, Schiff, having been interested by the apparent synchronism between the swelling of the spleen during digestion and the occurrence of trypsin in large quantities in the pancreatic juice or infusions of the pancreas, formulated, in 1862, a definite theory of a splenic-pancreatic relationship. His deductions were drawn from the results of a series of experimental inquiries. The most important of these were (1) experiments in which the tryptic activities of pancreatic infusions from normal animals were compared with those from animals with the spleen removed or functionally cut off by ligature of the splenic pedicle, and (2) experiments in which the amounts of digested albumin introduced into the duodenum (either with the duodenum ligated at both ends or in duodenal fistulas) were tested in normal and splenectomized dogs. His results led him to believe that after extirpation of the spleen, anatomically or functionally, trypsin fails to appear in the pancreatic juice or in an infusion of the gland during that stage of digestion in which it is normally present. He concluded that "die eiweissverdauende Kraft des Pankreas in jeder Verdauungsperiode durch die Milz und ihre Volumenzunahme bedingt wird." He then put forward the hypothesis, conforming to his

famous "peptogen" theory, that during congestion a substance is produced within the spleen which is carried away by the blood and gives to the pancreas the wherewithal to form its peptonizing ferment.

Lussana (1868), Schindeler (1870), Ewald (1878), Bufalini (1879) and Malassez (1881), by various methods of experimentation, were unable to demonstrate any impairment of the tryptic activity of pancreatic juice or infusions after splenectomy. Thus Schiff's research seemed discredited and his theory disproved.

The final acceptance of the part of the zymogens, discovered by Heidenhain and announced in 1872, threw all evidence thus far submitted out of court and necessitated a complete reopening of the subject. Herzen, who had formerly been Schiff's laboratory assistant at Florence and had confirmed his chief's results, tried to unravel the tangle caused by modifying Schiff's hypothesis. He argued thus (I am quoting, with slight modifications, his pupil Bellamy): Since the zymogen even in splenectomized animals is being continuously elaborated, and therefore independent of the spleen and its periodic congestion; and since zymogen accumulates in the gland cells during fast, but becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to the splenic dilatation, it seems feasible that the spleen produces by "internal secretion" during its congestion an unknown substance which, carried away by the circulating blood, transforms the inert zymogen, already deposited in the pancreas, into active trypsin. Herzen performed many experiments to demonstrate this. These experiments, *in vitro*, were tests of tryptic digestion in which he employed aqueous boric acid and glycerin infusions of the pancreas and spleen.

The digestive tests of Herzen were repeated by Carvallo and Pachon (1893), but with negative results. However, after communicating with Herzen, Pachon conscientiously went over his experiments and, with his collaborator, Gachet, was converted entirely to Herzen's point of view. Gachet and Pachon devised an intravenous injection experiment which became much used. By it they ascertained that good tryptic digestion by pancreatic infusions obtained from splenectomized animals could be secured only after the intravenous injection of an infusion of congested spleen.

Much less striking were the results of Badano (1900), who used both the infusion method of Herzen and the injection method of Pachon: yet his findings were confirmatory of those of these workers.

The crowning and ultimate effort made by the Herzen school is represented in the work and writings of Besbokaia and Bellamy. The latter considers the splenic internal secretion to be carried to the pancreas by the solid elements of the blood, and insists, as did

Herzen, "The pancreas of a dog deprived of its spleen exists in a condition of complete and permanent atrypsia."

Much in line with this so-called "freighting" theory of a pancreatic activating splenic hormone are the findings of Mendel and Rettger at Yale (1902-1903). From their work they concluded: "(1) Extracts of the spleen, prepared from the organ when congested during digestion, increase the proteolytic power of the pancreas. This was demonstrated *in vitro* and *in vivo*. (2) Injections of defibrinated blood from the splenic vein are likewise effective. (3) A boiled extract of spleen is ineffective. (4) Extracts of other tissues (liver, pancreas) apparently have little action. The same is true of pure saline infusions. (5) The precipitate produced by the addition of alcohol to active splenic extracts contains a trypsinogenic substance. (6) The extracts of the pancreas of splenectomized dogs are not always free from trypsin. Whether this is entirely attributable to an extrapancreatic transformation of trypsinogen is not determined."

A permanent pancreatic fistula, made by the technic of Pawlow, was first made use of in the study of this problem by Popielski (1901). He could find no activation of trypsinogen by any splenic ferment. Pawlow, under whom Popielski worked, states from his own observations that he considers Herzen to have greatly overrated the part of the spleen in pancreatic digestion and that Herzen's assumptions do not correspond with the facts.

A critical survey of the errors of previous investigators has been made by Silvestri (1901). As the result of a diligent series of researches he could not subscribe to the ideas of Herzen and Gachet and Pachon. He considered that the spleen favored the proteolytic power of pancreatic extracts by means of the kinase furnished by the leukocytes so abundant in this organ.

A novel and ingenious experiment was performed by Frouin in 1902. He isolated the stomach from the alimentary tract in dogs and then performed splenectomy. The removal of the spleen did not apparently interfere with the nutrition of the animals even when on a meat diet. He argued that since the nutritive condition of splenectomized animals remained excellent when gastric digestion was excluded, it was improbable that there had been any deficiency in the secretion of tryptic pancreatic ferment.

A histologic investigation of the effect of ablation of the spleen on the formation of zymogen granules in the alveolar cells of the pancreas was made by Tiberti in 1903. He could demonstrate no change following splenectomy.

In the endeavor definitely to settle the subject of a splenic-pancreatic relationship, Prym, in 1904 and 1905, carried on a most exhaustive series of researches. He used permanent pancreatic fistulas in the first investigation. From data thus obtained his most important conclusions were: The normal dog with a per-

manent pancreatic fistula, made according to the method of Pawlow, secretes after each feeding for each digestive period a pancreatic juice which contains only protrypsin if the juice is prevented from coming in contact with the intestinal mucosa by probing the duct; contact with the intestinal mucosa for a short time, or even the addition of small amounts of fresh intestinal juice, changes protrypsin into trypsin; the amount of proteolytic power of the pancreatic juice is not influenced in any recognizable way by splenectomy; intravenous injections of splenic infusions by the method of Gachet and Pachon have no influence on pancreatic secretion in the splenectomized dog with a permanent pancreatic fistula. In a second investigation Prym made use of pancreatic and splenic infusions as employed by Herzen. He found (as was also shown by Hekma) that when boric acid is used in the preparation of pancreatic infusions, bacteria play an important part in changing protrypsin into trypsin. When in like manner glycerin is used as a vehicle, the water content of the infusion is a matter of prime importance. In conclusion, he asserts that the spleen has no part in the activation of trypsinogen.

Further observations on two dogs with permanent pancreatic fistulas (Pawlow technic) were made by Lombroso and Manetta in 1915. From their results they were led to believe that the three enzymes of the pancreatic juice (trypsin, lipase and amylase) do not vary in any way after splenectomy, but that the amount of pancreatic secretion increases to a remarkable degree.

In the course of studies conducted on the general subject of the part played by the spleen in digestion, I have taken up again the question of a splenic-pancreatic relationship. This has been prompted by the conflicting results of the investigations just reviewed, by the allusions met with in scientific literature wherein the status of the Schiff-Herzen hypothesis is still assumed to be unsettled, and by the opportunity afforded by the perfection of a technic for the formation of a permanent pancreatic fistula which permits reducing sources of error to a minimum.

**Experimental Methods.** Observations were made on dogs with permanent pancreatic fistulas. The technic employed in making these fistulas has been given in detail in a previous communication.<sup>40</sup> Briefly, the salient features of the operative procedure are transplanting the duodenum under the skin of the abdomen with twisting of the duodenal axis to the right; severing the major pancreatic duct at its entrance into the gut; and bringing the duct to the surface through a stab wound in the skin away from the primary operative incision. This method gives fistulas which secrete a juice with inactive proteolytic ferment. Such a juice is much to be desired, since it permits of accurate activation of the trypsinogen after collection, and does not digest and erode the abdominal wall of the animal.



The pancreatic juice was collected by strapping the animals to a frame and applying a metal funnel over the duct opening. Three hundred grams of raw meat cut into small cubes were given as a secretory meal. At other times the diet consisted of dog biscuit and milk, and small amounts of soda bicarbonate were fed in order to make up for the alkali lost in the juice secreted from the fistula. The dogs were deprived of food for about eight hours and of water for two hours previous to beginning each experiment. Collections of juice were made for four or more hours after giving a secretory meal.

The amount of juice secreted hourly was measured and its proteolytic activity determined in all instances. Special experiments were conducted in which lipolytic and amylolytic fermentative power and the degree of alkalinity of the juice were ascertained.

The trypsinogen of the juice was activated into trypsin by the addition of an enterokinase solution prepared after the method of Bayliss and Starling; that is, by digesting the scrapings of mucosa of dog's duodenum in chloroform water for two days, then filtering, first through ordinary filter paper, and second through a Berkefeld filter. Mett's tubes, coagulated at 85°, were used to determine the tryptic digestive activity; 5 cc of pancreatic juice, 1 cc of enterokinase solution and two sections of Mett's tubes were placed in the thermostat at 39° for twenty-four hours. The results obtained were expressed directly in the number of millimeters of albumin digested (average of four readings).

The lipolytic activity was tested by adding 2 cc of pancreatic juice to 1 cc of neutral olive oil. The mixture was well shaken and placed in the thermostat at 39° for twelve hours. Then 5 cc of 95 per cent alcohol were added and the amount of fatty acids determined by titration with tenth normal sodium hydroxide, using phenolphthalein as an indicator. In the tables the lipolytic activity has been expressed directly as the number of cubic centimeters of tenth normal sodium hydroxide required to affect neutralization under these conditions.

Amylolytic activity was measured by a slightly modified Robert's method. The starch paste solution was boiled for five minutes. The iodine solution used was prepared by diluting 1 cc of a solution of: potassium iodide, 4 gm.; iodine, 2 gm.; water, 250 cc to 100 cc. One cubic centimeter of juice was placed with 100 cc of 0.1 per cent starch paste at 40° for three minutes; then 1 cc of the iodine solution was added to 1 cc of the mixture and the time noted when the achromic point was reached. After the achromic point had been obtained within four to six minutes after the addition of the enzyme the amylolytic activity was calculated by the formula

$$D = \frac{10}{V} \times \frac{5}{N}$$
 when  $V$  = volume of enzyme solution and  $N$  = time in minutes required to reach the achromic point.  $D$  is the number

of cubic centimeters of 1 per cent starch paste hydrolyzed to the end point in five minutes by 1 cc of juice.

Besides the unit concentrations of trypsin, lipase and amylase, comparative figures are tabulated representing the average total digestive unit of each enzyme secreted for each hour. These figures have been reached for trypsin and steapsin (since these ferments when determined quantitatively by these experiments obey the law of Schütz and Borissow for enzymic activity) by multiplying in each instance the square of the enzyme value or concentration for each hour by the amount of juice secreted that same hour; these results have been added, the sum divided by the number of days on which observations were made, and thus an average comparative amount for the total output of enzyme for each hour obtained. In the case of amylase a similar procedure was employed, save that the enzyme value on concentration was not squared, since in this instance the Schütz-Borissow law does not apply, but the amount of digestion varies directly with the concentration of the enzyme.

For the determination of the degree of alkalinity, 5 cc of pancreatic juice was incinerated, dissolved in 25 cc of distilled water and titrated with tenth normal hydrochloric acid, using phenolphthalein as an indicator. In the tabulation the alkalinity has been expressed by the number of cubic centimeters of tenth normal hydrochloric acid required to effect neutralization under these conditions.

After establishing a norm for the amount of pancreatic secretion and its ferment content, splenectomy was performed on three dogs, one of which died after the operation. Observations are also given on one animal which was not splenectomized. All operative procedures were conducted under ether anesthesia with the employment of sterile technic.

**Protocols.** D 697: A male mongrel in good condition, weighing 14 kg. A two-stage operation for pancreatic fistula was performed; the duodenum was transplanted under the skin May 27, 1920, and the fistula established July 21. The animal continued in good health and maintained its weight. Between September 6 and 20, however, during which time no observations were made and no prophylactic dilation of the fistular orifice performed, the pancreatic duct strictured and closed. September 22, the dog was etherized and an attempt made to reestablish the patency of the duct, but this proved unsuccessful and further continuance of the experiment was impossible (Table I).

D 701: A female mongrel in good condition, weighing 21.3 kg. May 28, 1920, a one-stage operation for pancreatic fistula was performed. The major pancreatic duct was quite small and divided into six branches close to its duodenal attachment. Pancreatic secretion from the fistula began four days later and con-

tinued normally until June 17, when a stricture occurred about 0.6 cm. from the orifice. A few days later the stricture was passed with a sound and a dilatation of the duct found behind it. From this time on the duct remained patent. There was a slight loss of weight. (Table II).

Splenectomy was performed July 7. Twelve hours later the animal died. At necropsy cause for death could not be found. The terminal portion of the pancreatic duct was dilated to twice normal size. The pancreas was normal. There were a few hemorrhagic areas in the omentum just proximal to the point of ligation of the splenic vessels. The common bile duct was dilated to four times normal size. There was a slight hypostatic congestion of the lungs.

D 719: A male mongrel collie in good condition, weighing 13.7 kg. June 5, 1920, a one-stage operation for pancreatic fistula was performed which was exceptionally successful. July 23, splenectomy was performed. The animal remained in excellent condition, although it had lost 2 kg. in weight at the end of two and one-half months. September 12, about three weeks after the close of the experiment, a continuous secretion of pancreatic juice appeared. Anorexia became marked and the animal lost weight rapidly and died September 22, three months and eighteen days after the establishment of the fistula. (Table III.)

At necropsy the pancreatic duct was found to be patent. The pancreas appeared to be normal. There was no accessory splenic tissue. A hair ball 5 cm. in diameter was found in the stomach.

E 130: A female mongrel in good condition, weighing 10.2 kg. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The fistula was eminently successful and the animal gained weight slightly. January 4, 1920, splenectomy was performed. Two weeks after the close of the experiment the duct strictured about 2 cm. from the surface; however, the patency of the duct reestablished itself without interference and pancreatic secretion from the fistula continued until the date of death. The animal gradually lost weight, and March 10, 1921, was killed by bleeding under ether on account of the marked inanition which had developed. The fistula had functionated three months and three days. (Table IV.)

At necropsy the pancreatic duct was found to be patent and the abdominal wall wet with pancreatic fluid. The pancreas was normal. Destruction of acinar tissue or pancreatic infection was not revealed by microscopic examination. There was no accessory splenic tissue.

**Review of Experimental Data.** The tables of experimental data show that in this set of experiments splenectomy caused no changes in pancreatic secretion which were definite and constant enough to justify the postulation of a functional splenic-pancreatic relationship.

In every instance the pancreatic juice collected did not contain active trypsin.

TABLE I.—DETERMINATIONS OF NORMAL PANCREATIC SECRETION OF DOG D 697—SECRETORY MEAL, 300 GM. OF MEAT.

1920.	Amount of secretion.							Trypsin (Mett's tubes).						
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	Sixth hour, cc.	Seventh hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	Sixth hour, mm.	Seventh hour, mm.
Aug. 11 . .	13.7	9.3	9.0	9.3	..	..	..	3.60	4.00	4.40	3.95			
Aug. 20 . .	23.5	15.2	17.1	13.0	15.0	13.8	7.2	2.40	2.95	3.20	3.90	4.20	4.0	3.7
Aug. 23 . .	7.0	5.0	10.8	11.5	6.4									
Aug. 26 . .	8.1	10.0	7.0											
Aug. 28 . .	10.5	24.0	37.5	44.8	29.4	18.4	16.0							
Sept. 1 . .	13.8	22.5	25.9	27.3	16.0	..	..	5.30	5.00	5.10	4.60	5.10		
Average . .	12.8	14.3	17.9	21.2	26.7	16.1	11.6	3.77	3.98	4.23	4.15	4.65	4.0	3.7

TABLE II.—DETERMINATIONS OF NORMAL PANCREATIC SECRETION OF DOG D 701—SECRETORY MEAL, 300 GM. OF MEAT.

1920.	Amount of secretion.							Trypsin (Mett's tubes).						
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	Sixth hour, cc.	Seventh hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	Sixth hour, mm.	Seventh hour, mm.
June 29 . .	10.4	38.0	24.0	14.4	..	..	..	3.1	2.8	3.50	4.0			
June 30 . .	7.8	11.0	7.6	11.5	18.8	13.2	..	3.5	4.2	4.10	4.4	3.90	4.7	
July 2 . .	51.6	41.3	27.8	12.5	..	..	..	2.5	3.0	3.80	3.6			
July 6 . .	21.0	11.0	30.0	29.2	17.7	20.7	19.8	2.6	2.3	2.40	2.5	2.40	2.5	2.4
Average . .	22.7	25.3	22.35	17.4	18.25	16.95	19.8	2.9	3.1	3.45	3.6	3.15	3.6	2.4

The results given in Tables I and II have been included to illustrate further the normal findings of pancreatic secretion under the conditions of this study and to serve as controls for the results in the splenectomized animals presented in Tables III and IV. In most instances the amount of pancreatic juice secreted was greatest within the first two hours after the secretory meal and rapidly decreased thereafter, so that the major portion of the secretion for each digestive period occurred within the first four hours. This agrees with the curve of pancreatic secretion on a meat diet given by Pawlow. The tryptic activity ordinarily was sufficient to digest from 3 to 4 mm. of albumin (Mett's tubes) in twenty-four hours; it fluctuated hourly and reached its height during the third and fourth hours.

TABLE III.—DETERMINATIONS OF PANCREATIC SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG D719.  
SECRETORY MEAL, 300 GM. OF MEAT.

1920	Amount of secretion.					Trypsin (Mett's tubes).					Steapsin $N_{10}$ NaOH for neutralization.					Alkalinity $N_{10}$ HCl.
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	First hour, mm.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	Fifth hour, mm.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	Fifth hour, cc.	
						BEFORE SPLENECTO MY.										
July 8 . . .	28.8	42.1	23.8	19.0	19.0	2.09	3.10	3.00	3.00	3.0	0.50	0.70	0.8	1.80	...	3.0
July 12 . . .	22.5	16.3	14.3	11.0	...	2.30	2.70	2.90	3.00	3.4	0.80	1.30	3.1	2.30	....	2.40
July 14 . . .	29.4	18.0	21.3	15.0	9.0	2.85	3.10	3.00	3.10	2.6	0.70	0.90	0.9	2.00	...	2.97
July 16 . . .	14.7	4.3	5.6	7.5	6.9	2.00	3.10	3.20	2.90	...	0.70	0.97	1.6	2.03	...	
July 19 . . .	28.7	98.5	2.7	2.4	...	2.40	2.75	...	...	3.0	0.70	0.97	1.6	2.03	...	
Average . . .	24.8	19.8	13.5	11.0	11.6	2.49	2.95	3.00	3.00	3.0	10	14	24	37		
Average total digestive units .	...	...	...	...	...	165	172	146	119	107						
						AFTER SPLENECTO MY.										
July 28 . . .	33.0	2.22	7.0	9.8	...	2.75	3.25	3.90	2.40	...	0.40	0.90	0.8	0.80	...	3.10
Aug. 2 . . .	14.0	8.50	11.4	9.1	...	1.70	1.90	1.20	2.80	...	0.50	1.00	1.6	2.80	...	2.40
Aug. 4 . . .	29.5	15.4	8.8	4.4	...	1.95	2.35	2.40	2.55	...	...	...	...	...	...	
Aug. 11 . . .	14.4	2.9	2.4	1.0	...	3.05	3.20	3.60	3.20	...	1.20	0.80	0.7	3.20	4.50	
Aug. 13 . . .	18.0	20.0	32.8	8.6	3.5	1.65	1.66	1.55	2.30	...	0.70	0.70	0.8	1.20	...	3.70
Aug. 16 . . .	32.0	7.7	6.1	2.3	...	2.00	2.70	2.70	...	...	0.90	0.80	1.2	...	...	
Aug. 18 . . .	25.3	12.5	9.6	4.2	...	2.60	2.35	...	...	...	0.40	0.50	...	...	...	
Aug. 20 . . .	18.3	10.0	...	...	...	...	...	...	...	...	...	2.50	...	...	...	
Aug. 23 . . .	20.5	11.0	7.3	6.6	...	...	...	...	...	...	...	...	8.5	...	...	
Aug. 26 . . .	12.7	6.4	4.0	6.0	...	3.10	3.80	3.70	3.40	...	1.90	1.30	0.5	0.70	...	
Aug. 28 . . .	26.6	20.6	8.6	7.0	...	...	...	...	...	...	...	...	...	...	...	
Sept. 1 . . .	32.7	24.0	9.4	12.0	...	4.10	3.30	4.70	2.80	...	0.67	0.95	2.0	1.74	4.5	3.07
Average . . .	23.1	13.4	9.8	6.5	3.5	2.54	2.70	2.97	2.78	...	24	18	51	34		
Average total digestive units	...	...	...	...	...	176	66	69	45	...						

TABLE IV.—DETERMINATIONS OF PANCREATIC SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG E 130, SECRETORY MEAL, 300 GM. OF MEAT.

Date.	Amount of secretion.				Trypsin (Mett's tubes).				Steapsin $\frac{N}{10}$ NaOH for neutralization.				Amylase (value of D).			
	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	First hour, min.	Second hour, mm.	Third hour, mm.	Fourth hour, mm.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.	First hour, cc.	Second hour, cc.	Third hour, cc.	Fourth hour, cc.
								BEFORE SPLENECTOMY.								
Dec. 20, 1920 . . .	24.5	11.0	6.5	2.5	3.90	3.60	3.85	3.90								
Dec. 24, 1920 . . .	22.3	12.2	7.3	8.3	4.20	4.70	4.90	5.00								
Dec. 27, 1920 . . .	18.2	4.5			2.80	5.40										
Dec. 29, 1920 . . .	17.5	12.5	6.3	5.8					3.50	6.50	7.00		16.0	22.2		
Dec. 31, 1920 . . .	25.7	18.4	13.0	6.0	4.45	4.80	5.00	8.20	10.00	8.30	7.00		20.9	28.6	30.8	111.1
Jan. 3, 1921 . . .	15.3	10.6	7.8	2.5	4.30	4.40	4.45	4.75	7.00	9.50	6.60		62.5	55.5	71.3	
Average . . .	20.6	11.5	8.5	5.0	3.93	4.58	4.55	5.46	6.83	8.1	6.86		49.7	53.2	51.0	111.0
Average total digestive units . . .					339	252	188	176	1200	920	426		624	464	478	666
								AFTER SPLENECTOMY.								
Jan. 7, 1921 . . .	20.0	11.0	7.5	10.0	3.50	4.15	4.50	4.50	4.30	3.00			20.0	44.4		50.0
Jan. 10, 1921 . . .	22.7	9.2	5.0	8.8	3.60	3.55	3.55	4.10	1.10	0.90			15.6	12.5	27.7	20.8
Jan. 12, 1921 . . .	41.5	40.8	34.2	17.8	3.80	3.80	4.20	4.20	3.00	1.80			17.9	13.9	20.8	25.0
Jan. 14, 1921 . . .	34.6	27.6	18.4	18.2	3.90	3.80	3.70	3.95	5.50	4.50			33.3	27.7	27.7	35.7
Jan. 17, 1921 . . .	30.6	24.7	30.0	14.0	4.00	4.40	4.90	4.70	1.40	2.40			31.3	27.7	41.7	35.7
Jan. 19, 1921 . . .	24.3	12.0	10.0	8.5	3.76	3.94	4.17	4.29	3.06	2.52			23.6	25.2	29.5	70.9
Average . . .	28.8	20.9	17.5	12.9												
Average total digestive units . . .					433	328	301	353	253	155	149	88	704	464	645	414

In Table III it is seen that the amount of secretion, the average concentration of trypsin and of steapsin, and the degree of alkalinity of the pancreatic juice were practically the same before and after splenectomy. However, when the average total digestive units are compared, it will be noted that there was a decrease in the total amount of trypsin secreted in the second, third and fourth hours, whereas the total amount of steapsin secreted was increased save in the fourth hour.

In Table IV it is seen that the amount of secretion after splenectomy was markedly increased, especially during the second, third and fourth hours; the concentration of trypsin was slightly decreased, that of steapsin and that of amylase very much so. However, when the average total digestive units are compared it is noted that the total amount of trypsin secreted was really increased, and the amount of amylase practically the same as before removal of the spleen, although the amount of steapsin was reduced.

Hence, when the many uncontrollable factors that must enter into experiments of this type are taken into consideration, it is realized that the minor changes that occurred after splenectomy might be expected. The increase in the amount of secretion (Table IV) may possibly be explained as resulting from disturbances in the splanchnic circulation due to the severance and ligation of the splenic artery and vein.

The changes in the secretion of trypsin are negligible and the data given seem to justify definite assertion that splenectomy exerts no influence on the trypsinogenic function of the pancreas. The amount of amylase secreted was the same after removal of the spleen as before. The amount of steapsin in one instance was slightly increased, in the other much decreased, thus on the whole showing no definite change; however, the same weight cannot be attached to the figures for steapsin as that given to the figures for trypsin and amylase, since the quantitative determination of lipolytic activity is much less accurate than the method of determination for tryptic and amylolytic power.

**Discussion.** In reviewing the experimental work on the relationship of the spleen and pancreas it is apparent that the researches and their results fall into two categories: first, that in which digestive experiments have been carried out *in vitro* with infusions of pancreas and spleen, and second, that in which the activity of pancreatic juice has been ascertained before and after splenectomy in animals with permanent pancreatic fistulas. In the first category the findings in most instances have been positive, and an increase in the proteolytic power of pancreatic infusions accrued from the addition of splenic extracts; in the second the results have been uniformly negative.

The explanation of this inconsistency may lie in several factors. When the proteolytic digestive power of pancreatic infusion is

tested with the addition of infusion of spleen many uncontrollable and as yet little understood elements are introduced. The spleen itself, as shown by Hedin, contains proteolytic enzymes, one acting in an acid medium and the other in an alkaline medium. It is doubtful whether these are of much importance in this connection. Of much greater significance probably are the unavoidable effects of bacterial contamination of the infusions leading to the activation of trypsinogen, as shown by Prym, and the influence of the high leukocyte content of the spleen, as suggested by Silvestri. Delezenne found a substance in leukocytes which could transform trypsinogen into trypsin, although its existence was later denied by Bayliss and Starling and by Hekma, who showed that enterokinase is produced only by intestinal mucous membrane. Opie states that the polymorphonuclear neutrophilic leukocytes and their ancestral granulated cells produce a ferment, leukoprotease, which, acting best in an alkaline or neutral medium, is similar to trypsin, though of much less activity. It is possible that this enzyme may play a part in such experiments as those under discussion. The whole question of the digestive effects of splenic extracts is surrounded by haziness, and the only definite statement to be made here is that splenic extracts should not be used therapeutically when more conclusive methods are available.

Permanent pancreatic fistulas furnish the means of approaching the problem of the relation of the spleen to the pancreas in a manner free from the drawbacks mentioned. All published investigations conducted with such fistulas have been negative. The present inquiry on the whole confirms these previous researches and justifies the statement that the spleen plays no part in the elaboration or activation of the proteolytic pancreatic ferment, trypsin.

**Summary.** The so-called Schiff-Herzen hypothesis in its final form assumed that during the digestive congestion of the spleen a substance is liberated into the blood stream which transforms the zymogen of the pancreas into active trypsin. Many experimental investigations have seemed to substantiate this theory; many others have seemed to invalidate it. The former have been digestive tests *in vitro* with the use of pancreatic and splenic infusions; the latter have been experiments on animals with permanent pancreatic fistulas.

In the present study data are given concerning the pancreatic secretion, before and after splenectomy, on two dogs with permanent pancreatic fistulas secreting an inactive proteolytic juice; and on two similar nonsplenectomized dogs serving as controls. Removal of the spleen in these instances caused no constant changes in the amount, enzyme content, or alkalinity of the pancreatic juice.

It is concluded from a review of the literature and this experimental inquiry that a definite trypsinogenic function of the spleen has not been demonstrated.



## BIBLIOGRAPHY.

1. Badano, F.: La digestione pancreatica dell' albumina nelle lesioni della milza. Osservazioni sperimentale. Clin. med. ital., 1900, 39, 109-122.
2. Bayliss, W. M., and Starling, E. H.: The Proteolytic Activities of the Pancreatic Juice. Jour. Physiol., 1904, 30, 61-83.
3. Bellamy, H. F.: On the Role Played by the Spleen in the Pancreatic Digestion of Proteids. Lancet, 1900, 2, 1185-1190.
4. Bellamy, H. F.: On the Agents Concerned in the Production of the Tryptic Ferment from its Zymogen. Jour. Physiol., 1901, 27, 323-335.
5. Besbokaia, Menia: Du rapport fonctionnel entre le pancréas et la rate. Lausanne, Wacchter-Gutzwiller, 1902, 58 pp.
6. Bufalini, G.: Sull' attività digerente del pancreas negli animali smilzati. In his: Rendic. d. ricerca sper. eseg. nel Gabinetto fisiol. d. r. Univ. di Siena. Siena, Bernardino, 1879, pp. 35-54.
7. Camus, L., and Gley, E.: A' propos de l' action de la rate sur le pancréas. Compt. rend. Soc. de biol., 1902, 54, 800-802.
8. Carvallo, J., and Pachon, V.: De l' activité digestive du pancréas des animaux à jeun, normaux et dératés. Compt. rend. Soc. de biol., 1893, 5, 641-645.
9. Carvallo, J., and Pachon, V.: Expériences sur le pouvoir digestif du pancréas dans l' état de jeûne chez les animaux normaux et dératés. Arch. de physiol. norm. et path., 1893, 5, 633-640.
10. Corso, F.: Il pancreas degli animali smilzati digerisce? Imparziali, 1878, 18, 193, 257, 298.
11. Delezenne, C.: Sur la distribution et l'origine de l'entérokinase. Compt. rend. Soc. de biol., 1902, 54, 281-283.
12. Duncan, D.: La chymie naturelle ou l'explication chymique et mécanique de la nourriture chez l'animal. Montpellier, 1683. Quoted by Gachet.
13. Ewald: Ueber Digestion mit Pankreas nach Milzextirpation. Arch. f. Anat. u. Physiol., 1878, p. 537.
14. Ferré, G.: Influence de la rate sur l'action digestive du suc pancréatique. Bull. Soc. d' anat. et physiol. de Bordeaux, 1890, 11, 238-240.
15. Frouin, A.: Influence de l'ablation de la rate sur la digestion pancréatique chez des animaux agastés. Compt. rend. Soc. de biol., 1902, 54, 418-419.
16. Frouin, A.: La rate exerce-t-elle une action sur la transformation intrapancreatique du zymogène en trypsine. Compt. rend. Soc. de biol., 1902, 54, 798-800.
17. Gachet, J.: Du rôle de la rate dans la digestion pancréatique de l'albumin. Bordeaux, 1897.
18. Gachet, J.: Digestion tryptique des albuminoïdes dans le duodénum de chiens normaux et dératés. Gaz. hebdom. d. sc. méd. de Bordeaux, 1897, 18, 486-488.
19. Gachet, J., and Pachon, V.: Existence et nature de la sécrétion interne de la rate à fonction trypsinogène. Compt. rend. Soc. de biol., 1898, 5, 364.
20. Gachet, J., and Pachon, V.: Nouvelles expériences sur la sécrétion interne de la rate à fonction pancréatogène. Arch. de physiol. norm. et path., 1898, 10, 363-369.
21. Gersten, A.: (Part of the Spleen in the Formation of Albumin Ferment of the Pancreas.) Vrach, 1901, 22, 1-6.
22. Gley, E.: Sur la signification de la splénectomie consécutive à l'extirpation totale de l'estomac. Compt. rend. Soc. de biol., 1902, 55, 419-421.
23. Gutschy, L.: (The Influence of the Spleen on the Pancreatic Juice.) Licce. vjestnik. u. Zagrebu, 1898, 20, 376-378.
24. Hedin, S. G.: Investigations on the Proteolytic Enzymes of the Spleen of the Ox. Jour. Physiol., 1903-1904, 30, 155-175.
25. Heidenhain, R.: Beiträge zur Kenntnis des Pankreas. Pflüger's Arch. f. d. ges. Physiol., 1875, 10, 557-632.
26. Heidenhain, R.: Herman's Handbuch der Physiologie, 1883, 5, 206.
27. Hekma, E.: Ueber die Umwandlung des Trypsin-Zymogens in Trypsin. Arch. f. Anat. u. Entwicklungsgesch., Physiol. Abt., 1904, pp. 343-365.
28. Herzen, A.: Sulla digestione dell'albumina effettuata dal succo pancreatico e sulla funzioni della milza. Imparziale, 1869, 9, 641, 738; 1870, 10, 97. Also transl. (Abstr.): Cong. med. de toutes les nations, Bologne (1869), 1870, 2, 387-392.

29. Herzen, A.: Della funzione digestiva della milza. *Imparziale*, 1877, 17, 321, 353.
30. Herzen, A.: Neue Versuche über den Einfluss der Milz auf die Bildung des weissverdauenden pankreatischen Saftes. *Centralbl. f. d. med. Wissensch.*, 1877, 15, 435.
31. Herzen, A.: Nouvelles experiences sur le rapport fonctionnel entre le pancréas et la rate. *Arch. de physiol. norm. et path.*, 1877, 4, 792-794.
32. Herzen, A.: Ueber den Einfluss der Milz auf die Bildung des Trypsins. *Arch. f. d. ges. Physiol.*, 1882-1883, 30, 295-307.
33. Herzen, A.: Rate et pancréas. *Compt. rend. Soc. de biol.*, 1893, 5, 814-817.
34. Herzen, A.: La fonction tryptinogène de la rate. *Interméd. de biol.*, 1897-1898, 1, 266.
35. Herzen, A.: Rapport sur les fonctions de la rate. In Schiff: *Ges. Beitr. z. Physiol.*, 1898, 4, 232-235.
36. Herzen, A.: Rôle tryptinogène de la rate. *Cong. internat. de méd.*, 1900, sect. de physiol., pp. 108-114.
37. Herzen, A.: Aelteres, Neues, and Zukünftiges über die Rolle der Milz bei der Trypsinbildung. *Arch. f. d. ges. Physiol.*, 1901, 84, 115-129.
38. Herzen, A.: Nouvelle phase de la question concernant les rapports fonctionnels entre rate et pancréas. *Rev. méd. de la Suisse Rom.*, 1904, 24, 548-552.
39. Inlow, W. D.: The Spleen and Digestion. Study I. The Spleen and Gastric Secretion. *AM. JOUR. MED. SC.*, 1921, clxii, 325-348.
40. Inlow, W. D.: A Technic for the Formation of a Permanent Pancreatic Fistula Secreting Inactive Proteolytic Ferment. *Jour. Lab. and Clin. Med.* 1921, vii, 86-90.
41. Levier, E.: Sécrétion interne de la rate. In Schiff: *Ges. Beitr. z. Physiol.*, 1898, 4, 366.
42. Lioni, G.: Sul modo di comportarsi della secrezione pancreatica ed epatica negli animali smilzati. *Riforma med.*, 1904, 20, 1381.
43. Lombroso, U., and Manetta, P.: Influenza della milza sulla funzione pancreatica. *Policlinico*, 1915, 22, sez. med., 117-129.
44. Lussana, F.: Intorno all'azione digerente del succo pancreatico sugli albuminoidi e intorno alle funzioni della milza. *Ann. univ. di med.*, 1868, 205, 416.
45. Lussana, F.: Della funzione digestiva della milza. *Gazz. med. ital. lomb.*, 1877, 4, 331.
46. Malassez, L.: Sur le pouvoir digestif du pancréas chez les chiens dératés. *Gaz. méd. de Paris*, 1881, 3, 145.
47. Mendel, L. B. and Rettger, L. F.: Experimental Observations on Pancreatic Digestion and the Spleen. *Am. Jour. Physiol.*, 1902-1903, 7, 387-404.
48. Opie, E. L.: Inflammation. *Harvey Lectures*, Philadelphia, Lippincott, 1909-1910, pp. 207-208.
49. Pawlow, I. P.: The Work of the Digestive Glands. (Trans. by W. H. Thompson.) London, Griffin & Co., 1910, pp. 164-165.
50. Popielski, L. B.: [The Spleen and the Albumin Ferment of the Pancreas.] *Vrach*, 1901, 22, 138-142.
51. Prevost, J. L., and Batelli, F.: Expériences relatives au rôle de la rate dans la digestion pancréatique de l'albumine. *Rev. méd. de la Suisse Rom.*, 1901, 21, 124-127.
52. Prym, O.: Milz und Pankreas. Versuche an Hunden mit permanenter Pankreasfistel. *Arch. f. d. ges. Physiol.*, 1904, 104, 433-452.
53. Prym, O.: Milz und Pankreas. 2 Teil. Versuche mit Infusen beider Organe. *Arch. f. d. ges. Physiol.*, 1904, 107, 599-620.
54. Prym, O.: Milz und Verdauung. *Verhandl. d. deutsch. Kong. f. innere Med.*, 1911, 28, 398-401.
55. Rusca, C. L.: Contributo sperimentale allo studio dei rapporti tra milza e digestione. *Gazz. med. ital.*, 1912, 63, 321, 331, 341.
56. Sajous, C. E. de M.: The Internal Secretions of the Pancreas and Spleen. *Internal Secretions and Principles of Medicine*. 9 ed. Philadelphia, F. A. Davis Co., 1920, 1, 362-420.
57. Schiff, M.: Ueber die Function der Milz. *Schweiz. Ztschr. f. Heilk.*, 1862, 1, 201, 397.
58. Schiff, M.: Sulle funzioni del pancreas e della milza. *Imparziale*, 1865, 5, 115-117.
59. Schiff, M.: Fonctions de la rate. *Cong. périod. internat. d. sc. méd. Compt. rend.*, 1878, pp. 47-49.

60. Schiff, M.: Ueber die Funktion der Milz. *Ges. Beitr. z. Physiol.*, 1898, 4, 167-222.
61. Schiff, M.: *Pancreas et rate. Recueil des memoires physiologiques.* Lausanne, Benda, 1898.
62. Schindeler, T. A.: Beiträge zur Kenntnis der Veränderungen des thierischen Organismus nach Milzextirpation. Greifswald, Hache, 1870, p. 30.
63. Silvestri, T.: Sulla funzione tripsinogena della milza. *Riforma med.*, 1901, Pt. I, 17, 843, 854, 868.
64. Silvestri, T.: Sulla pretesa funzione tripsinogena della milza. *Riforma med.*, 1902, Pt. IV, 18, 554-558.
65. Tiberti, N.: Osservazioni microscopiche sulla secrezioni pancreatiche negli animali smilzati. Sperimentale. *Arch. di biol.*, 1903, 57, 758. Also transl.: *Microscopische Untersuchungen über die Sekretion des Pankreas bei entmilzten Tieren.* *Beitr. z. path. Anat. u. z. allg. Path.*, 1904, 36, 184-191.

## THE SURGICAL ASPECTS OF DISEASE OF THE BILIARY TRACT.

BY ABRAHAM O. WILENSKY, M.D.

NEW YORK.

(From the Mount Sinai Hospital, New York.)

INFLAMMATORY disease of the gall-bladder—cholecystitis and cholelithiasis—is most commonly an affection of middle age, occurring with special frequency in women and closely associated with the incidence of pregnancy. Many cases probably originate early in life and persist with no or only vague and indefinite symptoms until some time later; manifestations are known to occur in very young children, as shown by the collected statistics of Montgomery and Wolf, and Friedenwald and Ulmann. Such diseased conditions of the gall-bladder and bile passages may, for practical purposes, be divided into those in which gall-stone formation does not occur and those in which the occurrence of calculi in some part of the biliary system outshines by its presence those other elements of the clinical picture which perhaps have a more important bearing than the stones themselves.

As one meets these conditions on the operating table the various pathological pictures which one encounters are essentially the following:

1. Gall-bladders of a normal size and shape which show a practically normal histological structure: The contents consists of a thin light-colored bile or more rarely a viscid darker bile, together with a variable number of stones. The gall-bladder contents are very frequently bacteriologically sterile.

2. Dilated gall-bladders showing a normal or only slightly abnormal histological structure and containing a single stone, which frequently is impacted in the neck of the gall-bladder or in the

cystic duct. The contained bile is rather thin and frequently is bacteriologically sterile.

3. Large distended gall-bladders the walls of which show moderate or marked grades of atrophy, especially of the mucous membrane and muscularis: There are usually a large number of various size stones which lie loosely in a large amount of thin bile. Stones may also be present in any of the ducts.

4. Gall-bladders in which infection has taken place, containing a thin pus or more rarely a thick, creamy pus with stones: The walls of the gall-bladder are thickened and edematous and the mucous membrane is very frequently gangrenous. Abscesses may be present in the wall of the gall-bladder, between it and the liver bed, or, more rarely, in the substance of the liver a short distance away. The stones contained in the gall-bladder may be numerous, indicating that conditions correspond to Groups 1 and 3, with an added infection, or only a single stone is present, indicating that a hydrops, as described in Group 2, has become secondarily infected. In all of these the cystic duct usually becomes shut off. Stones may be present in any of the ducts.

5. Gall-bladders which have shrunk to less than their normal size, and the walls of which show a chronic productive inflammation, frequently with areas in which the evidences of a more recent inflammatory reaction is discernible. The amount of pericholecystitis varies from a minimum to an excessive degree, in which it seriously hampers the necessary operative manipulations. The contents of the gall-bladder may consist only of stones or bile, which may or may not be purulent, or of both of these; or thick emulsions of cholesterin containing fragmentary stones are present. When the cystic duct is open and a probe can be passed into the hepatic and common ducts the condition represents the end-results of Groups 1, 2 and 3; when the cystic duct is obliterated the condition is the end-result of Group 4. It very rarely happens that the scarring and contracture has advanced so far that only a short stump represents the gall-bladder; such a finding represents a very near approximation to a natural cure, but only when no calculi are present in any part of the biliary apparatus.

6. Gall-bladders corresponding to any of these groups, and with which there is associated a swelling of the head of the pancreas; this includes the acute and chronic forms of pancreatitis.

7. Inflammatory gall-bladder conditions without the formation of calculi. The group includes the acute and chronic forms of catarrhal cholecystitis and the acute and chronic empyemata of the gall-bladder, both of these with and without various degrees of pericholecystitis. In the acute cases bacteria can usually be cultivated from the wall or from the contents of the gall-bladder.

8. Gall-bladders corresponding in structure to those in Group 5, but without stone formation. These represent the end-results of those in Group 7.

In any or all of these groupings the available knowledge indicates that the biological sequence of events may be one of three:

1. The pure infections indicated best in Groups 7 and 8. The element of any metabolic disturbance cannot enter unless there is a complicating non-calculous obstruction of the common duct. The affection begins as a catarrhal cholecystitis, progresses rapidly to suppuration or subsides more or less incompletely; when repeated recrudescences of infection are permitted the lesion terminates in the contracted and shrunken gall-bladder of Group 8.

2. The cases that originate in some disturbance of the cholesterol metabolism. Most often these are initiated by the physiological changes which accompany pregnancy. The hypercholesterinemia of pregnancy may reach to such a degree as to make futile the normal compensatory mechanism; then the supersaturation of bile with cholesterol bodies is reduced to the normal by a precipitation of stones in some portion of the bile passages, almost always the gall-bladder. If no further hypercholesterinemic crisis occurs, or if no infection supervene, these patients have symptoms which are due to the mechanical effects of the stones acting as foreign bodies.

3. Combinations of infection and disturbed cholesterol metabolism may occur either simultaneously or alternately, and with different degrees of severity: Depending on the factor which is paramount, on the intensity of the latter's manifestations, on the stage of the process, or on the presence or absence of the many complicating factors, which now become numerous, the pathological picture shows wide variations.

It must seem quite apparent and beyond argument that a careful consideration of the various pathological pictures portrayed in this communication must show that, once infection of any kind establishes itself in the gall-bladder—especially as is most often the case when stones are present—the resultant lesion is there to stay and that some mechanical means is necessary before it can be entirely eradicated. The various pictures are but stages of one another and the progression of the latter from the simpler to the more complex is but a matter of time and opportunity. Anatomical healing is rarely if ever complete, and most of the attempts toward its consummation result in increasing mechanical deformity which precludes the possibility of a natural and permanent relief of symptoms. And if the focus of infection be allowed to persist for any undue length of time its evil potentialities are quickly to be noted in neighboring organs, and the end-results include additional dangerous and sometimes unrelievable lesions, and are associated with increasing risks which attend an attempt at surgical relief.

Some newer studies have shown that associated changes are present in the liver itself. One sees this clinically in the easily palpable, enlarged, engorged, congested and edematous livers. Graham

has shown that in cases of acute and subacute cholecystitis there is constantly present the evidences of inflammation characterized by a leukocytic infiltration of the interlobular and periportal sheaths; in the more severe cases the infiltration extends to the peripheries of the lobules, and is associated with edema, slight grades of necrosis and moderate fatty degeneration. Organisms were quite commonly cultivated from the liver tissue. In chronic cholecystitis the liver often presents a picture practically identical with that of an early cirrhosis. The inflammatory reaction appears to be principally a pericholangitis. One can see the basis in these findings for the persistence of infection in the liver, and in some instances, undoubtedly, this state of affairs causes a recurrence of symptoms after an apparently successful operation. The stones which come from the intrahepatic ducts—intrahepatic cholelithiasis—are most probably due to a persisting bacterial infection of the ducts and liver parenchyma.

The finding of lesions resembling those demonstrable in the early stages of cirrhosis is of particular interest, inasmuch as it indicates the possibilities with long-continued and neglected foci of disease. The studies of Ogata indicate that these may be the response to the bacterial element of the clinical picture and those of Rous and Larrimore that they may result from obstruction of the biliary drainage system. In human pathology it is very probable that both of these factors functionate; commonly stasis of bile is associated with bacterial infection and the formation of connective tissue in the liver parenchyma will be much enhanced thereby. In intrahepatic cholelithiasis a form of biliary cirrhosis is quite common.

There is considerable evidence also that the pancreas is secondarily involved in neglected cases of disease of the gall-bladder and bile passages. Infection travels very easily along the lymphatics from the primarily involved biliary tract to the pancreas and the various forms of chronic pancreatitis are probably a response to bacterial toxins as they spread within the confines of the pancreatic gland. The spread of infection from the biliary tract is first along the lymphatics of the gastro-hepatic omentum to the lymph nodes along the upper border of the pancreas and then to the gland itself. If the attacks of cholecystitis or cholangitis should be allowed to continue and repeat themselves chronic changes in the pancreas ought to be expected. The lesions in the pancreas are not limited to these chronic forms of inflammation: it is a fairly common experience to witness the hyperacute emergency of a fulminating acute pancreatitis resulting from the impaction of an apparently insignificant calculus in the ampulla of Vater—a frequently fatal lesion which might have been entirely prevented if the original condition in the biliary tract had been previously corrected by operation.

There are other important and dangerous lesions which can result from neglected gall-bladder disease. These, while not very frequent, are still common enough to be serious menaces, and in any large hospital experience one sees several of these every year. The danger of a free perforation of an acute empyema of the gall-bladder is not slight, and although in the majority of the cases the process is walled off so that only a pericholecystitic abscess results, occasionally these protective adhesions are absent and a general peritonitis of a most violent form results. It is no uncommon thing for a large gall-stone to ulcerate through the gall-bladder wall into an adherent viscus; among the difficulties that then ensue the most formidable is a stubborn infection of the bile passages which, aside from the dangers of the actual operation or operations is usually sufficient to finally cause a fatality. All of these can be prevented entirely if the underlying gall-bladder disease be recognized at an early stage and submitted to operation.

For all of us, and especially for the internist and general practitioner, the most important question must necessarily be: How shall gall-bladder disease be diagnosed at an early stage—early enough to obviate completely all of the unnecessary complications which can occur when the focus of disease is not eradicated in time? There is, unfortunately, no method of precision available at present with which this purpose can be accomplished except in a deplorably minor number of instances. One must therefore rely on the general manifestations and on those elicitable data which by their presence are presumptive evidence of gall-bladder disease.

Of all the available data the history is most important. The value of the history is very great in all disease referable to the upper abdomen and becomes predominant in disease situated in the gall-bladder and bile ducts. The clinical groups can be segregated as follows:

1. Cases in which there are one or more attacks of gall-bladder colic separated by periods of good health. Very frequently the first attack occurs in pregnancy or early in the postpartum period. The clinical picture is sharply demarcated and should be apparent even to the tyro.

2. Cases in which these attacks punctuate a constant condition of ill-health the manifestations of which, were it not for the definite attacks of colic, would be vague and indistinct and of no special discomfort to the patient.

3. Cases of dyspepsia in which the bulk of the symptoms is referred to the stomach. When as in the previous groups there are distinct attacks of acute or subacute colic it is easy to recognize that there are reflex relationships to the gall-bladder and that disease of the latter is primarily at fault; but in the others

these tell-tale marks of gall-bladder disease are not present and other evidence is necessary to make the proper diagnosis.

4. Cases in which the chief complaint is right-sided abdominal pain of no special severity and bearing the characteristics of no special symptom-complex. The clinical picture has marked resemblances to the complexes associated with dislocated kidneys in young neurotic females; to that of some of the chronic forms of appendicitis; frequently to that of ureteral stone; to other forms of intra-abdominal disease or to purely functional states. Diagnosis is always difficult in these patients and frequently is only decided at an exploratory laparotomy. To the observant medical mind these various clinical pictures differ essentially in the presence or absence of definite attacks of biliary colic typical of that accompanying the attempted or consummated passage of a gallstone down in the cystic or common ducts. When these attacks are present and are observed by a competent practitioner, or when their description as given by the patient tallies accurately with our notions of what a gallstone colic should be, they furnish indubitable evidence of the presence of disease in the gall-bladder or bile ducts—perhaps the most important single piece of evidence of any which can be obtained.

5. A fifth group of cases includes those in which a single acute inflammatory condition appears in the upper right abdominal quadrant, characterized clinically by a sudden onset with generalized abdominal pain rapidly localizing in the right hypochondrium, with nausea and perhaps vomiting, with rigidity and tenderness and most frequently with a palpably enlarged, distended and tender gall-bladder. These are the acute empyema cases having marked similarities to acute appendicular attacks and with all the necessity which the latter have for early if not immediate operation. Necessarily these must not be associated with the presence of stones, and such pure infections, especially in men, form a very common variety of gall-bladder disease.

6. The sixth group includes those cases in which, besides the usual manifestations of some acute condition in the right hypochondrium, there is added the manifestations of a general infection; these are the cholangitis cases. The clinical picture includes chills and high fever, marked prostration and other signs of a high grade of intoxication; sometimes it is possible to cultivate bacteria from the blood stream. The very acute cases carry a grave prognosis and are frequently fatal; or the process assumes a less virulent and more subacute form, and is part of the picture of the more neglected varieties of disease of the biliary apparatus. The very acute forms are uncommon and are also known to occur as operative infections; the subacute and chronic forms are relatively more frequent. In the latter it is quite probable that the actual process does not extend very far beyond the major divisions of the



primary hepatic branches in the majority of patients. The chronic forms of cholangitis ultimately become associated with new connective-tissue formations, suggestive of a biliary cirrhosis.

The evidence obtained by physical examination of the patient is second in importance in the diagnosis of disease of the gall-bladder and bile ducts; the possible data may be of two kinds: (a) Entirely negative, or (b) partially or definitely positive. The definitive data which are obtainable are the presence of a palpable mass (gall-bladder), the local and general signs of peritoneal inflammation and the presence of jaundice. When this elicitable evidence is of a positive nature it is almost always so decisive as to make unnecessary any further examination of any kind in order to establish a diagnosis; this is most liable to occur in the acute cases. In the chronic cases the physical examination is disappointing in that it usually adds no data of any kind.

The laboratory evidence which is useful in the diagnosis of gall-bladder disease is that furnished by the roentgenological examination of the patient. But positive findings are, unfortunately, neither the rule nor very common, even when other obtainable evidence is conclusive. A liberal estimate of the positive findings seems to be in the neighborhood of 25 per cent, although in the literature the claims of various workers put the positive results as high as 90 per cent. Except in these fortunate instances the laboratory evidences yield no help whatsoever.

The method devised by Lyon, of Philadelphia, is still in an experimental stage; the method holds promise. But much more work is still necessary to remove what sources of error are still present in order to put the method upon a basis reliable enough for general use in practical medicine.

To anyone who sees the actual pathology of disease of the gall-bladder and bile ducts exposed on the operating table day after day as outlined in this communication, it seems futile to say other than that these diseases are essentially surgical and susceptible of cure only by surgical means; medical treatment can at best be only palliative. And if the lesson can be learned, especially by the medical men who naturally see these cases first, of the great necessity of operating upon these patients at the earliest possible period of the disease—and that means as soon as possible after the diagnosis has been established—very much can be accomplished in a preventive way. Those who have opportunities of seeing the late results with their many unnecessary complications—and these are no uncommon things even now—need very little urging to bring their patients early to the surgeon; and the rest should learn by the experience of these others that the best way of curing the serious complications in the liver and pancreas, and the most efficient way of lowering the risks of any operative intervention, is by their total obviation in an efficiently done operation at an early period of the malady.

One should not be led astray by the enthusiasm of Lyon as regards the value of the intraduodenal use of magnesium sulphate as a therapeutic measure. The method is naturally limited and useless in cases in which the cystic duct is obstructed by calculus, by inflammatory adhesions or by extraneous masses, such as enlarged lymph glands or tumors; or in states of hydrops, or when a mass of inspissated bile or calcareous material completely fills the gall-bladder. Cholelithiasis, or acute, inflammations leading to acute and chronic empyema with or without gangrene, or any condition of a more complicated nature than the simplest, are entirely beyond the reach of this method. For such conditions the method, at best, can exhibit only slight degrees of palliation. Perhaps the only application of this therapeutic measure will be found in states similar to catarrhal jaundice.

The question as to the best form of surgical treatment for gall-bladder and biliary tract disease not only resolves itself into a discussion of the indications and contraindications of cholecystectomy as against those for cholecystostomy, but also into a discussion of the value of some form of biliary drainage. As a rule the long list of indications that one commonly observes in the literature, for which cholecystectomy is required, reads like a *resume* of the various pathologies to which the gall-bladder and biliary ducts are subject. To recapitulate these, cholecystectomy is indicated:

1. For acute and chronic empyemata of the gall-bladder, or for gangrenous gall-bladders, or for any gall-bladder inflamed to such an extent that complete restitution to the normal is not likely or even possible.

2. For hydrops or any similar condition in which a stone is impacted in the cystic duct, stricture formation in the duct, which is almost sure to follow, will prevent the permanent closure of any fistula.

3. For chronically inflamed gall-bladders with or without stones or for those thickened to such a degree that collapse of the wall is not possible to the extent of permitting a spontaneous closure of any fistula resulting from a cholecystostomy.

4. In cholelithiasis even when the gall-bladder wall shows very little or no pathological change.

5. For malignant conditions.

There is one further indication which increasing experience has shown both to include and outshine every other indication for cholecystectomy. There is constantly increasing evidence of the fact that a much superior permanent result is obtained in any instance in which a cholecystectomy is done as opposed to cholecystostomy, so that the best opinion at the present time is that a gall-bladder which is diseased enough to give sufficient symptoms to warrant an operation is one of little or no value, or is a menace to the patient's future health by reason of its potentialities for

trouble and should always be entirely removed. This restricts the usefulness of cholecystostomy markedly and its field is found in certain associated conditions, such as pancreatitis. Here the indication is drainage of bile, but even this can be accomplished through a choledochotomy opening.

It is true that in any of the cases cholecystostomy may be unavoidable, because of its supposed lesser shock and operative risk as an emergency measure—let it be emphasized—not because of the essential nature of the pathology, but because of the enfeeblement due to age or associated disease or to the deterioration of the general resistance powers due to neglected primary or complicating conditions brought to operation at a comparatively late period. Under such conditions cholecystostomy is only a palliative measure. There is much evidence to prove the statement that in competent hands the manipulations necessary for cholecystectomy under ordinary conditions, and in the average run of cases, are not so very much more productive of shock than those necessary for cholecystostomy; what difference there is, is probably due to lessened resistance on the part of the patient, and whatever little added risk is present is more than compensated for by the very great superiority of the more permanent result.

The operation of cholecystectomy fulfils a double purpose:

1. It removes a local focus of infection. When the latter is strictly limited to the gall-bladder this can be completely done and the effect is permanent. In the cases, however, in which the focus of infection has spread beyond the limits of the gall-bladder itself, either into the ducts or perhaps into the liver substances, surgical removal of the entire infected area is not feasible or possible, and a complete cure follows only when efficient drainage is adequately carried out.

2. It removes the biliary reservoir with its contained stones and stagnated, infected and changed bile. The latter represents part of the end-products of any disturbed metabolism which may have antedated the operation; there is no effect upon the metabolic activities themselves. In order to obtain any effect upon the latter it is necessary to institute bile drainage either by leaving the stump of the cystic duct open (an inefficient method) or by making an additional opening into the common or hepatic ducts (a most efficient method).

The operation of cholecystostomy accomplishes the following objects:

1. Bile drainage is a necessary concomitant and sequel to this operation; hence, cholecystostomy enables a better removal of the end-products of disturbed metabolism. Practically this results in a depletion of the cholesterol content of the blood (Wilensky and Rothschild) and is a beneficial effect upon the metabolic activities.

2. Cholecystostomy affords a surgical method, inferior to chole-

cystectomy for draining the infected area. This does not presuppose that the focus of infection in the gall-bladder has been removed, and apparent healing may take place before this source of infection has completely disappeared. Recrudescences of infection may therefore be expected and do actually occur; they form one of the important causes for the recurrence of symptoms after operation.

The escape of bile through a common duct biliary fistula is always complete for a variable length of time until the subsidence of inflammatory swelling and some dilatation of the duct permit a certain amount of bile to trickle into the duodenum; clinically this is demonstrated in the color of the stools. On the other hand the escape of bile through a gall-bladder fistula is complete only when there is associated a complete obstruction of the common duct or papilla of Vater, so that between these two common-duct drainage is much more efficient.

The effects of bile drainage have been summarized by Wilensky and Rothschild as follows:

1. With common-duct drainage the system is rapidly depleted of the accumulated products of an abnormal metabolism.

2. Gall-bladder drainage does not accomplish this extreme effect unless there be a concomitant obstruction in the common bile duct.

3. These effects are only obtained when the operation is properly done and all obstructions have been removed.

The good effect of bile drainage upon a disordered metabolism is probably in the nature of a recuperative process, founded upon the removal of abnormal amounts of excretory products; this seems to have marked similarities to the phenomena of fatigue and rest in muscle tissue associated with the accumulation and discharge of excretory bodies produced by cellular activity.

To these effects may be added:

4. Bile drainage is also an invaluable adjuvant in the control of any focus of infection in the intrahepatic biliary apparatus. For this purpose it is frequently necessary to continue it for many months' time.

The continued loss of bile from a biliary fistula has a deleterious effect upon the body. The symptoms that are likely to appear include: (a) Disturbances of digestion frequently associated with vomiting; (b) constipation of varying degrees due to an absence of bile from the intestinal tract; (c) depreciation in the general condition of the patient conducive to a lessened general resistance to any kind of trauma. These effects may be prevented by collecting the escaping bile and feeding it to the patient by the stomach tube.

The drainage of bile is one of the most important factors in any operation upon the gall-bladder and bile ducts. We have

all learned to value the procedure extremely highly. To recapitulate: it decreases the engorgement in the liver; it depletes the body of any associated products of disturbed liver metabolism and exhibits a beneficial effect upon these activities; it is the only method we have for overcoming any retained focus of infection in the liver; what is more, it covers up and rectifies any fault of technic in the removal of stones and enables the spontaneous discharge of small intrahepatic calculi as these pass downward into the extrahepatic ducts; and what is most, by virtue of all of these it prevents many recurrences of symptoms and many secondary operations.

No drainage of any kind following cholecystectomy has been advocated by a number of men. Willis and Bottomley have published experiences with this technic. The disuse of drainage means and presupposes a careful dissection and separate ligation of the cystic duct and vessels and of a careful and painstaking aseptic technic. In this regard operative technic is repeating the experiences which were gone through in the earlier days of appendix surgery. I have referred to this refinement of technic on several previous occasions. Too little attention has been devoted to the possibility of a cleaner and safer technic in gall-bladder and common-duct surgery. This is no new practice and there is no reason why there should not be certain cases in which drainage of any form can be safely omitted. In this regard the gall-bladder has many analogies to the appendix; one does not drain every case of appendicitis, and wide experience has taught us when the drainage can be safely omitted. Experience in gall-bladder surgery is not so abundant as regards the omission of drainage, and until it is so, the insertion of a drain is perhaps a more conservative measure. I am quite sure that many times these drains are unnecessary, as evidenced by a lack of any discharge through the drainage tube and by the fact that the tubes can be safely removed at the end of twenty-four to forty-eight hours. A tube for so short a period of time in no wise delays the convalescence or the healing of the wound; certainly, it is the safest way of doing things, and the precaution would perhaps save the occasional patient that died of hemorrhage, leaking or infection.

Owing to the results of biliary infection, which is practically always present, and the fact that operation still comes comparatively late, the prognosis of interference for common-duct stone is generally unfavorable. In operating attention should first be given to the common duct, as this carries the greater urgency; attention is given secondarily to the gall-bladder if the condition of the patient and other factors permit.

Most of the literature on the surgery of the common bile duct emphasizes two points essential to a safe outcome: (a) That the common duct itself be well drained, and (b) that the abdomen be drained down to the line of suture. It has been pointed out,

and quite rightly, that the infected ducts should be drained, as infection elsewhere is drained, and that closure of the common duct is not without the danger of leakage of infected bile. The possibility of closing the incision in the common duct for the sake of securing a cleaner and safer technic has been discussed by Richter; the common duct is a suitable drainage tube in itself by which the affected parts above may be drained if its patency is assured. Under any circumstances, however, the following conditions are, according to Crile, contraindications to the closure of the opening previously made in the common duct: (a) If there has been a stone in the papilla; (b) if the duct mucosa has been so injured as to cause hemorrhage; (c) if there is a probability of post-operative closure of the duct by swelling; (d) in the event of the probability that stones will come down from the liver; or (e) in conditions of marked disturbance of the liver metabolism. These various contraindications do not leave a very large field in which the refinement of technic advised by Richter can be considered if one takes into account the character of these various exceptions; at least one of these indications for drainage is almost sure to occur after almost every common-duct procedure.

In competent hands the mortality of uncomplicated gall-bladder operations is very small, certainly not more than 2 or 3 per cent. With the association of complicating conditions this becomes much higher; the mortality is highest in common duct obstruction by calculus. With the latter the mortality seems to depend on the following factors:

1. The age of the patient apparently has some influence, inasmuch as most of the patients who die are over fifty years old. Van Beuren's figures showed that the operation was more dangerous in men, as shown by a 45 per cent mortality among men and an 18 per cent mortality among women.

2. I quite agree with Gibbon and others that the mortality in gall-bladder infections depends very largely on whether or not a cholangitis is present; a cholangitis is one of the real dangers of gall-bladder disease. A patient having undoubted symptoms of gall-bladder infection should not be allowed to postpone operation because of this danger; the danger, if a true cholangitis develop, is one to life; in those fortunate cases in which it does not prove fatal the convalescence is prolonged and tedious. The high mortality of gall-bladder operations occurs in the cases with long-standing symptoms, with acute exacerbations of infection and with complications.

3. The mortality has direct mathematical relationships with the length of time for which symptoms are present before operation. The longer the symptoms are present the more chance for a fatality. The immediate severity of the symptoms before operation apparently makes no difference. For the general practitioner this point is

of the utmost importance, as it shows the very great necessity of bringing patients of this type to operation at the earliest opportunity. No amount of time spent in emphasizing this extremely necessary point should be considered wasted.

4. The presence of complications—pneumonia or pulmonary congestion, chronic or acute pancreatitis, nephritis, peritoneal abscesses, myocarditis or affections of the coronary arteries—increases materially the mortality. This goes hand-in-hand with the previous statement, inasmuch as if the patients are brought to operation early many of these complications can be obviated, or at least their intensity will not be enhanced by the continued presence of the inflammatory and infectious process in the gall-bladder and biliary tract.

5. There is no doubt that the skill of the operator is an important factor in these difficult operations: the length of time of the operation, the degree of trauma, the knowledge and ability to handle the technical difficulties, are all important factors in the mortality statistics. All of these, while perhaps of little importance in the average operation, become of extreme importance in the complicated, late or neglected forms of gall-bladder and bile-duct disease.

In cases of recurring symptoms after primary gall-bladder operations sufficient to warrant secondary explorations a variety of lesions are found. The most frequently found include (a) adhesions of various kinds; (b) stone in the gall-bladder or ducts or both; (c) persistence of infection; (d) biliary fistulæ; (e) common-duct obstructions of various kinds, including malignancies; and (f) chronic pancreatitis. In some of the cases more than one of the conditions enumerated are found.

Adhesions of one kind or another are found in all of the recurrent cases. The symptom-producing adhesions are very few in number, and are principally those that result in a partial obstruction of the pylorus or first portion of the duodenum. The symptoms caused by this deformity include those of the ordinary forms of cicatricial pyloric stenosis. The simple separation of adhesions is usually followed by only temporary relief. Gastro-enterostomy, or, better still, a procedure similar to the Finney pyloroplasty, is superior to the separation of adhesions in these cases. In an old case of extensive adhesions the operation of separating the latter and covering the resultant denuded surfaces is likely to be a very difficult procedure, attended with great risk of tearing the duodenum, and in some instances the colon. If a duodenal fistula result a most dangerous and difficult proposition is present with which one must deal; and in order to guard its proper repair, gastro-enterostomy with some form of unilateral pyloric exclusion is almost always advisable.

The second most common cause for the recurrence of symptoms

is the presence of stone or stones. The failure to remove all the gallstones at the primary operation is the most potent cause for the recurrence of any symptoms. It is not always easy to determine whether these recurrent stones were overlooked at operation or whether they had actually formed again after the primary operation. The impression, however, is strong that in a few instances at least, reformation has taken place. On the other hand it is not always possible at operation to clear the two primary branches of the hepatic duct. Again, as in the attempt to remove a stone or stones from the hepatic duct, one or more may be displaced upward beyond the reach of the surgeon and thus later produce common-duct obstruction, which requires re-operation. Complete and prolonged drainage after the primary operation is essential for a preventive cure, and one should not hesitate to open the common or hepatic ducts to secure it; this applies perhaps with even greater force to the recurrent cases.

The third most common cause of recurrence of symptoms is the persistence of infection. Most often this happens after cholecystostomies. Non-calculous cholecystitis is a clinical entity distinct from the type associated with the formation of stones and justifies the removal of the gall-bladder.

Cases occur also of non-calculous, non-malignant duct obstruction due to structure, to scar tissue or to ulceration. The principles involved in the treatment of these forms of common-duct obstruction are practically the same; the duct is laid open to the extent of involvement and drainage is provided in addition to whatever other procedures are found necessary. Resection of the diseased portion and end-to-end anastomosis is best; anastomosis of the proximal end of the duct with the duodenum, with or without mobilization of the latter, after the several methods proposed, is the next best operation; reconstruction of the duct after the Sullivan method is a poor third best.

Biliary fistulæ are practically all the result of stone in the stump of the cystic duct or in the common duct; the fistula can be obliterated only by removing the cause.

Chronic pancreatitis, according to Deaver, also causes post-operative symptoms; for these drainage is very essential and should be carried out for comparatively long periods of time.

Duct drainage is also indicated, and is imperative in cholangitis which results from gall-stone disease; it must be continued for a number of weeks.

It is important to know that after cholecystectomy dilatation of the extrahepatic ducts is the rule and is to be expected. In the early and late periods after operation it is not uncommon for the ducts to become suddenly hyperdistended, possibly from some unidentifiable spasm of the sphincter; a clinical picture then results resembling minutely a typical attack of gall-bladder colic



with pain, vomiting and even jaundice and fever. Sometimes it is extremely difficult to differentiate these temporary hyperdistensions from the mechanical effect of the passage of a stone. That this can occur has been proved at secondary explorations.

The great variance between recurrences after radical surgery of the gall-bladder and those that take place after conservative surgery leads to the manifest conclusion that radical treatment gives the greater prospect of a permanent cure. For the present, however, radical surgery, although it may fall short of being ideal surgery, is the best means one has of removing a pathological condition and its pernicious effects. In general most authorities agree with this viewpoint. Gall-bladders should always be removed at the time of the primary operation, as their retention in the presence of persisting infection come to represent an infected focus from which the system is intermittently flooded with toxins. If in these cases secondary cholecystectomy is refused by the patient, chronic pancreatitis may develop in addition to the chronic cholecystitis and invalidism may develop for the remainder of the patient's life.

#### REFERENCES.

1. Bottomley: Boston Med. and Surg. Jour., 1920, 183, 232.
2. Crile: New York State Jour. Med., 1920, 20, 333.
3. Deaver and Reimann: Jour. Am. Med. Assn., 1920, 74, 1061.
4. Gibbon: AM. JOUR. MED. SC., 1918, 155, 644.
5. Graham: Surg., Gynee. and Obst., 1918, 26, 521.
6. Ogata: Jour. Med. Research, 1919, 60, 103.
7. Lyons: Jour. Am. Med. Assn., 1919, 73, 980. AM. JOUR. MED. SCI., 1920, 159, 553; 1920, 160, 515. New York Med. Jour., July, 1920.
8. Richter: Jour. Am. Med. Assn., 1919, 73, 1750.
9. Rous and Larrimore: Jour. Exper. Med., 1920, 31, 609.
10. Van Beuren:
11. Willis: Jour. Am. Med. Assn., 1917, 69, 1943; 1921, 76, 712.
12. Wilensky and Rothschild: AM. JOUR. MED. SC., 1918, 156, 404 and 564.

#### THE ETIOLOGY OF PNEUMONIA.\*

By RUSSELL L. CECIL, M.D.

NEW YORK CITY.

WHEN the physician has made a clinical diagnosis of pneumonia there are several questions which immediately present themselves for solution. Is it primary pneumonia or is the pneumonia secondary to some preëxisting pathologic condition? Is it lobar pneumonia or bronchial pneumonia? How many lobes are involved?

\* Read before the New York County Medical Society, March 28, 1921.

Finally, and in some respects the most important question of all, Which of the various bacteria are responsible for the infection?

I am aware that many clinicians will disagree with me on the relative importance of the bacteriology of pneumonia. Strangely enough, these same clinicians will admit the necessity for bacteriologic information in other infectious diseases but deny its importance in pneumonia. We are accustomed to make early and thorough examinations for the infectious agent in meningitis; we are accustomed to bacteriologic examination in dysentery and other intestinal infections. Even in endocarditis, arthritis and certain other rarer infections, we are anxious to find the etiologic agent.

Why, then, have we been so long in coming to a realization of the importance of a bacteriologic diagnosis in pneumonia? I think there are two reasons for this lack of interest: (1) Because the bacteriology of pneumonia has been one of the last branches of this subject to be worked out accurately, and (2) because there has been no specific treatment for pneumonia. Neither of these reasons, however, hold good at the present time. The various groups of pneumococcus and streptococcus have been accurately defined. Furthermore, we have a specific treatment for pneumococcus type I pneumonia and there are good reasons for believing that an efficient specific therapy will soon be worked out for the other types. Then, too, the prognostic value of a bacteriologic diagnosis in pneumonia has not been sufficiently emphasized. In respect to prognosis the microorganism present has great significance: For example, *Bacillus Friedländer* pneumonia is nearly always fatal. The mortality rate in pneumococcus pneumonia varies greatly with the type. As worked out by Dochez and Gillespie at the Rockefeller Institute the rate for pneumococcus type III pneumonia may be as high as 50 per cent. On the other hand, pneumococcus type IV shows a rate of only 10 to 15 per cent. A similar divergence is found in streptococcus pneumonia. *Streptococcus hemolyticus* pneumonia has a death-rate varying from 40 to 60 per cent, whereas *Streptococcus viridans* pneumonia is one of the mildest forms encountered. In our Camp Upton series the death-rate for *Streptococcus viridans* pneumonia was under 10 per cent.

It would appear from these figures that in many instances the type of bacterium present had a more important bearing on the prognosis in pneumonia than either the character or the extent of the consolidation. Personally, if I must have pneumonia I am indifferent whether it shall be lobar pneumonia or bronchial pneumonia, nor am I particularly concerned whether I have two lobes or three lobes involved; but I do care very much whether my infection is caused by *Friedländer's* bacillus or pneumococcus type IV. Furthermore, if streptococcus is the causative agent I am very anxious to know whether it is *Streptococcus hemolyticus*

or *Streptococcus viridans*. There is the difference here between 1 in 2 chances and 9 in 10 chances for recovery.

**Bacteriology of Pneumonia.** Practically speaking, there are only three bacteria that are commonly concerned in the etiology of pneumonia: *Pneumococcus*, *streptococcus* and *Bacillus influenzae*. Friedländer's bacillus, *Staphylococcus aureus*, *meningococcus* and other microorganisms are occasionally responsible for this disease, but they constitute such a small percentage of the whole that they must be looked upon as rarities.

The *pneumococcus* is the usual cause of lobar pneumonia. Dochez and Gillespie have classified pneumococci on the basis of their biologic characteristics into four groups. Thus all strains of *pneumococcus* type I cross-agglutinate and cross-protect. The same with types II and III. Group IV is the heterogeneous or waste-basket group and is composed chiefly of unrelated strains which do not fall into the other three groups. The first three groups are known as the "fixed types" of *pneumococcus*. They are highly parasitic as a rule, and except for type III rarely occur in healthy mouths. The strains that compose group IV are less virulent and are frequently encountered in healthy mouths.

At the time the studies on *pneumococcus* types were carried out at the Rockefeller Institute the fixed types were responsible for about 80 per cent of all lobar pneumonias, the remaining 20 per cent being caused by the group IV strains. During the two big epidemics of influenza this proportion was considerably upset by the relative increase in group IV pneumonias, but it is interesting to note that during the winter 1920-1921, in 200 cases of *pneumococcus pneumonia* typed at Bellevue Hospital the distribution has been as follows:

<i>Pneumococcus</i> type I . . . . .	86 cases	43.0 per cent.
<i>Pneumococcus</i> type II . . . . .	39 "	19.5 "
<i>Pneumococcus</i> type III . . . . .	34 "	17.0 "
Total . . . . .	159 "	79.5 "
<i>Pneumococcus</i> group IV . . . . .	41 "	20.5 "

It is clear from these figures that the disturbance in the incidence rate produced by the influenza epidemic was only temporary and that the incidence of the fixed types of *pneumococcus pneumonia* is the same now as it was before the epidemic of influenza occurred.

The *streptococcus* is the organism most frequently found in bronchopneumonia. Here, again, we must classify into the "hemolytic" and "viridans" groups. *Streptococcus hemolyticus* causes a severe form of lobular pneumonia very frequently complicated by multiple abscesses and empyema. *Streptococcus viridans* is often recovered from the small patches of terminal bronchopneumonia discovered at autopsy in cases of chronic systemic disease. Apart from this association with terminal broncho-

pneumonias, however, the *Streptococcus viridans* produces a very mild form of pneumonia, the mortality rate being less than 10 per cent. It is rarely complicated by empyema. It should be emphasized that both types of streptococcus pneumonia usually occur as a complication or sequel to some preceding disease or injury. During the war the hemolytic streptococcus attained such a high degree of virulence that it appeared in some instances to excite a primary pneumonia, but such cases were exceptions to the rule.

The influenza bacillus also produces a characteristic type of pneumonia, best exemplified by the nodular hemorrhagic pneumonias so frequently seen during the big epidemic. Unfortunately for the pathologist this organism rarely occurs in pure culture, so that it is often difficult to say just what part of the process is due to the influenza bacillus and what part to the other bacteria present. A study, however, of the occasional cases of pure *Bacillus influenzae* pneumonia and comparative studies on experimental *Bacillus influenzae* pneumonia in monkeys indicate that this microorganism is capable of setting up a bronchitis and bronchiolitis with peribronchial consolidation—in other words a true bronchopneumonia with hemorrhage and edema, sometimes succeeded in the later stages by emphysema and bronchiectasis.

The rarer forms of pneumonia will not be discussed at the present time. The Friedländer bacillus produces a typical lobar pneumonia usually fatal, fortunately rare. *Staphylococcus aureus* pneumonia is another unusual form, described by Chickering<sup>1</sup> as a purulent bronchopneumonia with abscesses. Like *Bacillus Friedländer* pneumonia it is usually fatal.

**The Mode of Infection in Pneumonia.** The pneumococcus, like most other bacteria, attacks the human host through the nose or mouth. The mere presence of virulent pneumococci in the pharynx is not sufficient, however, to excite a pneumococcus pneumonia. It is quite possible that the bacteria reach the trachea through the inspired air. Recent experiments<sup>2</sup> indicate that lobar pneumonia is bronchiogenic rather than hematogenous in origin. The constant production of the disease in monkeys by intratracheal injection and the constant failure to produce it by subcutaneous or intravenous injection are believed to be conclusive evidence that infection in lobar pneumonia takes place not through the blood stream but by way of the respiratory passages. The hematogenous theory has apparently depended upon the clinical observation of cases in which the pneumococcus was shown to be present in the blood at the time of onset of clinical symptoms of pneumonia or in occasional instances before the clinical symptoms of pneumonia had appeared. That the interpretation of this observation

<sup>1</sup> Jour. Am. Med. Assn., 1919, 72, 617.

<sup>2</sup> Blake, F. G., and Cecil, R. L.: Jour. Exper. Med., 1920, 31, 403, 499.  
VOL. 164, NO. 1.—JULY, 1922

as indicative of the hematogenous origin of pneumonia is incorrect, is established by the fact that in pneumonia experimentally produced by the intratracheal injection of pneumococcus the organisms have appeared in the blood stream within six to twenty-four hours after injection— frequently before clinical evidence of pneumonia or elevation of temperature have developed.

When a monkey is injected intratracheally with virulent pneumococci and killed a few hours later it can readily be demonstrated that in experimental pneumonia, at least, the initial invasion of the lung occurs somewhere comparatively close to the hilum. The earliest inflammatory changes are found here and microscopic sections taken through this region show pneumococci penetrating the walls of the large bronchi and invading the peribronchial and perivascular lymph spaces. Furthermore, sections from the same lungs taken nearer the periphery show no pneumococci in the lumina of the bronchioles or alveoli, but they may be present in large numbers in the alveolar walls. It is quite clear that invasion and spread of pneumococci in the lung in lobar pneumonia is by way of the perivascular, peribronchial and septal tissue and lymphatics and that the alveolar structure is primarily infected by spread of the pneumococci from the grosser framework of the lungs into the alveolar walls. With further advance of the process to the stage of hepatization, pneumococci pass out from the alveolar walls into the alveolar spaces together with the exudate. Although by no means an absolute rule, hepatization usually occurs first in the posterior and upper parts of the lower and in the posterior parts of the upper lobes. This distribution in no way precludes early extension of the consolidation as far as the pleura, since the pleura is comparatively near the large bronchi and vessels in the part of the lobe proximal to the hilum. As the disease progresses, hepatization spreads to the distal portions of the lobe until complete or nearly complete lobar consolidation has occurred.

Experiments with *Streptococcus hemolyticus* on monkeys<sup>3</sup> indicate that the mode of infection in streptococcus pneumonia is similar to that in pneumococcus pneumonia. The infection is bronchiogenic and primarily affects the interstitial framework of the lung. The reaction of the tissue to the streptococcus is different, and therefore the pathologic picture is different, but the mode of infection is apparently the same for the two infections.

Coming now to the influenza bacillus a different mechanism appears to be at work.<sup>3</sup> In *Bacillus influenzae* pneumonia the infection travels down the bronchial tree into the bronchioles and subsequently involves the neighboring alveoli by contiguity. Influenza bacilli are present in large numbers in the bronchioles and to a less extent in the adjacent alveoli. They are rarely found in any part of the interstitial tissue, and as MacCallum has pointed

<sup>3</sup> Blake, F. G., and Cecil, R. L.: Jour. Exper. Med., 1920, 32, 401.

<sup>4</sup> Ibid., 719.

out the lymphatics are noticeably free from involvement in *Bacillus influenzae pneumoniae*. This may explain why the influenza bacillus rarely invades the blood stream. The influenza bacillus lacks the invasive character possessed by the pneumococcus and streptococcus, consequently the lesions produced by this organism are local while those produced by pneumococcus and streptococcus involve extensive areas. The influenza bacillus, growing in a sense outside of the body, injures chiefly contiguous parts, probably by means of toxic substances which it secretes. The pneumococcus and streptococcus, invading the lymphatics, reach all parts of the lung and excite a massive lesion.

**The Epidemiology of Pneumonia.** In the United States pneumonia is an endemic disease, though it also occurs in epidemic form. The United States census for 1900 shows that more than 10 per cent of all deaths are due to some variety of pneumonia, and statistics seem to indicate that the incidence is increasing. In view of the fact that so many healthy individuals are pneumococcus carriers it was formerly assumed that most cases of pneumonia were auto-genous infections. During the past few years, however, important studies on the epidemiology of pneumonia<sup>5</sup> have been carried out at the Hospital of the Rockefeller Institute, the results of which may be briefly summarized here.

In a study of 398 normal individuals type I and type II pneumococcus were practically never encountered in the buccal secretions. Type III, on the contrary, was found in 11 per cent of the cases. Group IV was encountered most frequently, appearing in 27 per cent of normal salivas. In contrast to these figures the Rockefeller Institute investigators showed that in a series of 454 cases of lobar pneumonia either pneumococcus type I or type II was present in 62 per cent of the cases. Type III was present in only 13 per cent, group IV in only 20 per cent of the cases; in other words, the pneumococci most commonly found in the mouth secretions of normal individuals give rise to a minority of cases of lobar pneumonia. This appears to indicate that pneumonia due to types I and II does not arise from infection with the pneumococcus which is carried in the mouth, but that infection with these organisms occurs from without.

A study was also made of the types of pneumococcus present during convalescence in pneumonia. This study revealed the fact that only in exceptional instances does one find for a considerable time after recovery the same type of pneumococcus with which the individuals was infected during the disease. Usually the infecting organism was found to have disappeared in three or four weeks after the illness. After its disappearance either no pneumococcus is present or the infecting type has been supplanted by one of the types usually found in normal saliva. These obser-

<sup>5</sup> Stillman, E. G.: Jour. Exper. Med., 1916, 24, 651; *ibid.*, 1917, 26, 513.

vations afford still further evidence that infection in pneumonia occurs from without.

*Pneumococcus Carriers.* Carriers of virulent pneumococci probably play an important part in the dissemination of the disease. The Rockefeller Institute workers showed that a considerable percentage of persons intimately associated with patients suffering from pneumonia harbor in their mouths pneumococci of the same type as those in the patient. Whereas pneumococcus types I and II are almost never found in normal salivas, it was shown that in a large series of healthy individuals in contact with cases of lobar pneumonia 13 per cent were pneumococcus type I carriers and 12 per cent pneumococcus type II carriers. It was also shown that pneumococcus is more frequently present in the dust of rooms in which pneumonia has occurred than in those in which no pneumonia has existed. Moreover the type of pneumococcus found in the dust corresponds to the type of pneumococcus found in the patient.

All that has been said in regard to the epidemiology of pneumococcus pneumonia probably applies with equal force to Streptococcus hemolyticus pneumonia. Although the hemolytic streptococcus is often found in normal tonsils, it is reasonable to suppose that it exists there in a comparatively harmless form. The epidemics of streptococcus pneumonia are probably caused by a few strains of virulent streptococcus which are passed on from one case to another by carriers or by actual contact. The contagious character of erysipelas, tonsillitis, puerperal fever and scarlet fever (probably a streptococcus infection) all support the idea that in streptococcus pneumonia as it existed for example in the army camps, the disease is transmitted from man to man by direct or indirect contact.

**Methods of Making a Bacteriologic Diagnosis in Pneumonia.** The bacteriologic examination of the sputum can be accurately made in many cases by direct plating of the material on blood agar. This method, however, is slow and for that reason undesirable. The mouse method is undoubtedly the quickest and at the same time the most reliable method of determining the type of organism in pneumonic sputum. By this method a positive diagnosis can usually be made in twelve to eighteen hours. 0.5 cc of washed sputum emulsified in sterile normal salt solution is injected intraperitoneally into a white mouse. If pneumococcus is present an agglutination test can be performed at once on the peritoneal exudate and the type determined. If the infectious agent be streptococcus or Bacillus influenzae, or even Friedländer's bacillus, the mouse exudate will indicate it, for the peritoneum of the mouse is an ideal culture medium for all of these bacteria.

The Krumwicde method of examining the sputum is quick and reliable, but gives information only concerning the three fixed types of pneumococcus.

The Avery method is accurate when one uses very clean sputum in which the pneumococcus is present in practically pure culture. Unfortunately specimens of this character are not often obtained.

When sputum is not obtainable the diagnosis of pneumococcus types I, II and III pneumonia can sometimes be made very promptly by a precipitin test on the urine. Positive reactions, however, are usually obtained on severe cases only.

Other and less frequently available methods of making the diagnosis are by blood culture, lung puncture, examination of pleural and spinal fluid, etc. Examination of the sputum, however, remains the method of choice.

**General Remarks.** An accurate bacteriologic examination of the sputum is necessary before serum treatment can be rationally applied. If pneumococcus is demonstrated the type must be determined. If pneumococcus type I is present the administration of type I serum is to be seriously considered. The value of serum treatment has not yet been demonstrated for the other types.

In case *Streptococcus hemolyticus* is present the physician must watch the circulation and be on guard for abscess and empyema. On the other hand if nothing but *Streptococcus viridans* is present in the sputum, the prognosis is excellent. The influenza bacillus will only rarely be found in pure culture, but its presence in large numbers should be considered significant. In such cases there is danger of slow resolution and chronic bronchitis with occasionally emphysema and bronchiectasis.

In cases in which resolution is delayed the sputum should always be searched for tubercle bacilli. In cases of relapse a complete retyping is indicated, as relapses are often infections by a different microorganism.

The time has come when medical men should think of pneumonia in terms of the causative agent rather than in terms of anatomy or pathology—important as the latter aspects of the disease are. In consideration of the facts above presented, it would seem that the character of the infectious agent in pneumonia were more significant than the location or the type of consolidation. It is difficult at best to make accurate distinctions between lobar and lobular pneumonia, or to say in every case just how many lobes are involved in the process. On the other hand we now have at our disposal accurate and rapid methods for the determination of the infecting organism in pneumonia, and these methods are available to all practitioners, certainly to all practitioners in the larger cities. Would it not therefore be a step in advance to speak less of lobar and bronchial pneumonia and more of pneumococcus, streptococcus and *Bacillus influenzae* pneumonia? The writer believes that progress in the specific treatment of pneumonia is in large measure dependent upon the adoption of such a point of view.



THE INTRODUCTION OF ANTIMENINGOCOCCUS SERUM BY  
CISTERN PUNCTURE. REPORT OF A CASE OF MENIN-  
GOCOCCUS MENINGITIS IN AN INFANT AGED FOUR  
MONTHS CURED BY THIS METHOD.\*

BY A. GRAEME MITCHELL, M.D.

AND

J. J. REILLY, M.D.

PHILADELPHIA.

(From the service of Dr. J. P. Crozer Griffith, Children's Hospital of Philadelphia.)

As much as the employment of Flexner's serum has helped to reduce the mortality and lessen the number of sequelæ in meningococcus meningitis, nevertheless the death-rate is still high and residual injury occurs in a definite percentage of cases. Anyone who has witnessed such end-results of cerebrospinal infection as hydrocephalus, idiocy, paralysis, blindness and deafness will welcome any procedure which offers promise of lessening these consequences of infection in the ventricles and subarachnoid space.

There are several causes for the failure of serum treatment of meningococcus meningitis. Thus the particular strain of meningococcus acting as the infective organism in a given case may not be represented in the serum used; the virulence of the organism may be so great that the serum is of no avail; the serum may be given late in the course of the disease when the destructive processes already present would result in the death of the patient or in permanent brain injury, even though the causative organisms were destroyed. These sources of failure have been pointed out by Ayer.<sup>1</sup> It must be remembered that antimeningococcus serum operates chiefly as a bacteriolytic agent and must be brought into contact with the organisms it is intended to destroy. Herein lies the explanation of many failures of serum treatment.

It would seem, then, that there are three ways by which the treatment of meningococcus meningitis might be improved: (1) By making serum which will be as polyvalent as possible; (2) by administering serum early in the infection; (3) by so introducing serum that it will be brought into better contact with the causative organisms. In this connection it might be well to speak of the fact that serum may be given intravenously. Indeed, it has been claimed that almost 70 per cent of the cases of meningococcus meningitis show evidence of generalized infection and that

\* Read before the Section on Medicine of the College of Physicians of Philadelphia, November 28, 1921.

<sup>1</sup> Arch. Neurol. and Psychiat., 1920, 4, 529.

the mortality can be greatly reduced by combining intravenous with intraspinal serum treatment.<sup>2</sup>

Our concern in this presentation is with the mode of introducing serum into the subarachnoid space. Heretofore there have been two points of entrance to the cerebrospinal system—between the lumbar vertebræ and through the fontanelle into the ventricles. Except for rare accidents, lumbar puncture has been without danger, and serum introduced by this route is curative in many cases. Subarachnoid block and the consequent failure to obtain fluid by lumbar puncture has been the indication for ventricular puncture. Ventricular puncture with the introduction of serum has increased the percentage of cures and also is apparently harmless if properly performed. After the closure of the fontanelle the ventricular point of attack is complicated by the fact that trephining is necessary. Some clinicians have gone so far as to recommend that ventricular puncture and the introduction of serum into the ventricles should be employed as a routine method in infants whenever the diagnosis of meningococcus meningitis is made.<sup>3</sup>

As has been stated, the chief cause of failure when serum is given in the lumbar region of the spinal cord has been the inability, at times, to bring it into contact with all the infected surfaces of the subarachnoid space. It is in such cases—when the subarachnoid space is blocked by exudate, whether in the spinal canal, the cisternæ, the foramina or over the convexity of the brain surface—that ventricular puncture has been indicated and that cistern puncture will also be found of use.

There are reasons why cistern puncture would be a method of choice if it could be shown that it is, if not devoid of danger, at least as safe as lumbar or ventricular puncture. Ayer after performing forty-three punctures in 20 cases believes that it is a harmless procedure if carefully carried out. The greatest amount of exudate in meningitis is often at the base of the brain in the cisternæ. It is from adhesions in this region that communicating hydrocephalus develops,<sup>4 5</sup> and it is probable also that the internal type of hydrocephalus may be caused by the spread of exudate and adhesions from the cisternæ into the foramina rather than from the ventricles into the foramina. By injection into the cisternæ magnæ the serum, in concentrated form, is brought directly into contact with the most infected portion of the subarachnoid space without the necessity of traversing the spinal canal or passing from the ventricles through the foramina and thence into the cisternæ. However, while cistern puncture should quickly gain widespread

<sup>2</sup> Haden, R. L.: *Arch. Int. Med.*, 1919, 24, 514.

<sup>3</sup> Caussade, L. and Remy, A.: *Paris méd.*, 1921, 11, 129.

<sup>4</sup> Blackfan, K. D.: *Am. Jour. Dis. Children*, 1919, 29, 525.

<sup>5</sup> Dandy, W. E.: *Johns Hopkins Hosp. Bull.*, 1921, 22, 67.

use as a method of treatment in subarachnoid block, it will not be adopted as a regular route of approach in treating meningitis until its safety and efficacy have been further tested.<sup>6</sup>

The technic as described by Ayer<sup>7</sup> is as follows: "The patient is placed on the side, as if for lumbar puncture, with the neck moderately flexed. Care is taken to maintain the alignment of the vertebral column to prevent scoliosis and torsion, and in cases in which comparative pressure readings are important the lumbar and cisterna needles should be on the same horizontal plane. After antiseptic preparation of the skin, usually including the shaving of a little hair and local anesthetization with procain, the thumb of the left hand is placed on the spine of the axis and the needle inserted in the midline just above the thumb. The needle may be pushed rapidly through the skin, but should then be cautiously and guardedly forced forward and upward in line with the external auditory meatus and glabella until the dura is pierced.

"If the cisterna be entered at this angle there is usually a distance of from 2.5 to 3 cm. between the dura and the medulla, as shown on frozen sections; with the needle less oblique in position the distance between the walls of the cisterna becomes progressively less. Therefore it is good practice to aim a little higher than the auditory meatus, and if the needle strikes the occiput, to depress just enough to pass the dura at its uppermost attachment to the foramen magnum. At its entrance the same sudden 'give' is felt as in lumbar puncture.

"The needle employed is a regular lumbar puncture needle, nickeloid, 18 gauge preferred, with bevelled stylet, sharp on the sides but not too sharply pointed. There is rather less variation in the depth of the tissue traversed than in the lumbar region, being in an ordinary-sized adult 4 or 5 cm., the greatest distance in the series being 6 cm. and the smallest 3.5 cm. It was found that a faint circular scratch on the needle, 6 cm. from the tip, was entirely satisfactory in judging the distance, and was preferable to the deeper markings of the Patrick needle, which tend to make its insertion a little jerky and consequently less guarded."

In infants and children there are some slight modifications of this technic. Thus the distance from skin to cisterna is somewhat less—being about 2.25 to 3.5 cm., depending on the age of the patient. A needle smaller than 18 gauge may be necessary at times, although a fairly large caliber needle is preferable to allow for the flow of thick and viscid cerebrospinal fluid. It has seemed to us that the "give" of the needle on entering the cisterna magna is greater than that which is experienced in successful lumbar puncture, and one should be cautious not to exert too much

<sup>6</sup> See discussion of Dr. Ayer's paper in Arch. Neurol. and Psychiat., 1920, 4, 465-469.

<sup>7</sup> Loc. cit.

pressure, lest the sudden entrance of the needle carry it too far in a forward direction.

While cistern puncture has been done on animals<sup>8 9</sup> and for obtaining material at autopsy for some time, its use in the living human subject has been reported only by Wegeforth,<sup>10 11</sup> Ayer and Essick. It might be said in passing that the cistern has been drained after trephining at the base of the skull for the relief of meningitis.<sup>12</sup>

We wish to put on record our experience with cistern puncture in a case of meningococcus meningitis. Previous to the employment of cistern puncture in this case we had carried out the procedure on the cadaver with and without the skull-cap removed, and also in several cases of tuberculous meningitis. In this latter condition the usual temporary relief of symptoms of increased intracranial pressure was noted exactly as would occur after lumbar puncture. Since treating the case of meningococcus meningitis, we have used cistern puncture in a case of streptococcus meningitis and also in 2 cases of pneumococcus meningitis, but then only for diagnosis.

**CASE REPORT.** J. B., Italian, male, aged four months. Admitted to the Children's Hospital of Philadelphia, service of Dr. J. P. Crozer Griffith, March 15, 1921. On admission the infant was partly breast-fed and partly artificially-fed with a cow's milk mixture. Throughout the entire illness this combined feeding was continued.

*History of Present Illness.* For two weeks prior to admission the patient had been apparently in a febrile state, although the temperature had not been taken to verify this statement of the mother. The baby did not seem very ill until five days before admission, and the fever before this may have been due to a left otitis media, which had been discharging at times for about six weeks. Three days before admission convulsions, described as generalized, began, and these had recurred at frequent intervals since that time. The exact number of convulsions could not be determined, but they were evidently of frequent occurrence, as well as of different grades of severity.

No history of the symptoms other than those enumerated above could be elicited. There had been no vomiting or other gastrointestinal disturbance. The absence of vomiting is to be remarked, since this symptom is one of the earliest and most constant signs of meningitis, being in our experience more frequent than convulsions.<sup>13</sup> The child seemed drowsy between the convulsive

<sup>8</sup> Dixon, W. and Halliburton, W.: Jour. Physiol., 1913, 47, 215.

<sup>9</sup> Weed, L.: Jour. Med. Research, 1914, 31, 21.

<sup>10</sup> Wegeforth, P.: Ayer, J. B. and Essick, C. A.: AM. JOUR. MED. SC., 1919, 157, 789.

<sup>11</sup> Loc. cit.

<sup>12</sup> Haynes, I. S.: Arch. Pediat., 1913, 30, 84.

<sup>13</sup> Mitchell, A. G. and Falkener, W. W.: New York Med. Jour., 1918, 107, 103.

seizures, but nursed from the breast and bottle fairly well. The mother was not intelligent enough to have noted such conditions as hyperesthesia or rigidity. The past medical history, including the details of the patient's birth, was uneventful, the patient having been born at full term by easy labor.

On admission the baby seemed quite sick. The temperature was 101° F., the pulse 150 and the respiration 48. Examination of the heart, lungs and abdomen revealed no abnormal findings. There was, however, marked retraction of the head as well as a positive Kernig sign in both legs and other evidences of cerebrospinal irritation, such as increased knee-jerks, a positive Babinski reflex on both sides and a definite Brudzinski sign. A suggestive tache cérébrale was present. No ankle-clonus could be elicited. Pus was discharging from the left external auditory meatus. The pupils were equal and reacted slightly to light. The fontanelle was not bulging or tense—in fact, there was a slight depression in this region. Lumbar puncture performed at this time was unsuccessful, as fluid was not obtained.

March 16. On this date lumbar puncture resulted in obtaining only 2 cc of a very thick, yellowish fluid which showed the meningococcus in the stained smear, and later the organism was found on culture by Dr. A. G. Waltz. After the removal of the fluid 1 cc of antimeningococcus serum was introduced with difficulty.

March 17. The first convulsive seizure since admission occurred on this date. By lumbar puncture 1.5 cc of thick pus were obtained. After irrigation of the spinal canal with physiologic sodium chloride solution, 1.5 cc of antimeningococcus serum were introduced.

March 18. During all this time the physical findings described on admission were present and the fontanelle remained depressed and under normal tension. Because of the evident subarachnoid block and the absence of a bulging fontanelle it was decided to do cistern puncture rather than ventricular puncture. A needle introduced after the manner described by Ayer at first failed to obtain fluid. A stylet was introduced into the needle. When the stylet was withdrawn it was followed by a long string of material resembling nothing so much as tenacious nasal mucus. Immediately after this a stream of turbid spinal fluid flowed from the needle under considerable pressure; 9 cc of this fluid were removed and 6 cc of antimeningococcus serum were then slowly introduced. The specimen obtained by cistern puncture showed the meningococcus on smear and culture; contained albumin and globulin in large amount; had 2900 cells to the cm. and did not reduce boiling copper solution.

March 19. Lumbar puncture was not successful in obtaining fluid. By cistern puncture 17 cc of turbid fluid were removed under marked pressure; 5 cc of serum were introduced. A few

hours after the cistern puncture the patient had convulsive twitchings of the face and extremities.

March 20. Twelve cc of cloudy fluid were obtained by cistern puncture and 8 cc of serum were introduced.

March 21. Rigidity was still present, although not as marked as on admission. The fontanelle continued to be slightly depressed. Vomiting of a projectile character occurred for the first and only time while the child was under observation. On this date also it was noticed that the sclera of the left eye was injected. Subsequently the left eye developed panophthalmitis. Permission to remove the eye was refused and the condition eventually subsided with a subsequent atrophy—the right eye fortunately remaining normal. (The eye had been examined and treated by Dr. H. M. Langdon and Dr. A. R. Renniger.)

March 22. Eight cc of almost clear fluid were obtained by cistern puncture and 6 cc of serum were introduced. No meningococci were found in this fluid.

March 24. On this date it was decided to try lumbar puncture again, with the result that 7 cc of somewhat blood-tinged fluid were obtained under slightly increased pressure. No serum was given. A cistern puncture was then done. After the removal of 2 cc of clear fluid, which did not seem to be under increased pressure, the patient suddenly became shocked—the respiration ceasing for almost fifty seconds and the pulse being practically imperceptible. The needle was immediately withdrawn and the return to a normal pulse and respiratory rate was rapid.

March 26. Six cc of clear fluid under normal pressure were obtained by lumbar puncture. No serum was given. No meningococci were found.

April 15. By this time the baby's general condition had greatly improved. There was still slight rigidity of the neck, but other signs of cerebrospinal irritation were not present. No puncture had been performed since the one in the lumbar region on March 26.

April 26. The patient was discharged on this date, cured of meningococcus meningitis. There was atrophy of the left eye and a shrunken condition of the tissues of the orbit.

Six months after discharge from the hospital the patient was seen and examined. With the exception of the atrophy of the left eye the cure was apparently complete and no evidence of cerebrospinal irritation, optic atrophy, hydrocephalus or paralysis could be found.

We have reported this case because we desire to call attention to the applicability of cistern puncture to infants, and because, as far as we have been able to ascertain, this is the first case of subarachnoid block due to the meningococcus which has been cured by cistern puncture.

# REPORT OF A CASE OF DISSEMINATED GUMMATOUS SPOROTRICHOSIS, WITH LUNG METASTASIS.\*

BY LOUIS M. WARFIELD, A.B., M.D.

MILWAUKEE, WIS.

DISEASES due to certain varieties of fungi are claiming more and more attention. Scattered through the literature are many case reports and careful bacteriologic investigations of actinomycosis, blastomycosis, streptothricosis, sporotrichosis, etc. Some of the fungus diseases are primarily pathogenic for animals, and only now and then produce disease in man when conditions are favorable. Many of the forms of fungi occasionally pathogenic for man are, in their natural state, saprophytes on dead vegetables, bark of trees, hay, etc. Gradually the various forms have been differentiated one from another until now there are numbers of well-recognized mycelium-bearing fungi which may cause even fatal disease in man. Among these Gougerot gives an important place to the sporotrichum. In an address delivered in 1913<sup>1</sup> he gives six reasons why sporotrichosis should claim attention:

1. Because of its extreme frequency (in France, at least) and of its universal distribution. There is no part of the civilized globe which has not had its case or cases. In France over 200 cases were reported in the literature from 1906 to the end of 1910. Since then no one reports his cases unless there is something unusual about them.

2. Because of the practical importance from both prognostic and therapeutic standpoints of a correct diagnosis. He cites a number of cases in which the patients were given several months to a year rest-cure under the diagnosis of pulmonary tuberculosis. In 1 case reported a man had had a hip-joint amputation, then a forearm amputation was advised but refused. Diagnosis was corrected and the patient was well in six weeks. One case had severe pharyngeal ulcerations which were thought to be syphilitic. Mercury had been given, with no relief. Diagnosis was finally corrected and the patient was soon cured.

3. Because of the polymorphism of the disease there is no tissue exempt from its ravages, including bone.

He makes three main groups with subgroups:

- I. Disseminated sporotrichosis.

- (a) Disseminated gummatous non-ulcerating variety of the skin.

\* Read at the Meeting of the Association of American Physicians, Atlantic City, May 10-11, 1921.

<sup>1</sup> Gougerot: Sporotrichosis, Jour. State Med., London, December, 1913, 21, 705-768.

(b) Subcutaneous ulcerating tuberculoid gummata.

(c) Ulcerating syphiloid gummata.

(d) Polymorphous sporotrichosis.

II. Localized sporotrichosis.

III. Extracutaneous sporotrichosis—osseous, ocular, visceral, etc.

4. Because of the great ease in diagnosis one does not need a laboratory nor does he need to be an expert bacteriologist. He does need, however, tubes of glucose-agar. By inoculating a tube with some of the purulent material in the ulcers or abscess and placing it aside at room temperature for four to ten days the microscopic appearance is characteristic.

5. Because of the almost certain healing of even the most extensive lesions by the internal administration of KI, necessitating no loss of time by the patient from his daily occupation.

6. Because in the intensive study of the disease a new impetus was given to the study of mycotic diseases in general.

The honor of calling attention to the pathogenicity of the sporotrichum goes to B. F. Schenck,<sup>2</sup> of Johns Hopkins, who in 1898 published an article in the *Bulletin of the Johns Hopkins Hospital* on "Refractory Subcutaneous Abscesses Caused by a Fungus Possibly Related to the Sporotricha." He isolated and grew out the organism which has since been known by the name of *Sporothrix Schenckii*. In 1900 Hektoen and Perkins published a long article on the sporotrich. The first case published in any other country was that by de Buermann in 1903. Four years elapsed with the report of only 4 cases seen by de Buermann and Gougerot, then the *Bulletin et mémoires de la Société médicale des hôpitaux de Paris* was full of reports. From that time cases have been reported from various countries and from most of the states in the United States. Hyde and Davis,<sup>3</sup> of Chicago, reported on the disease in 1910.

In 1912, Ruediger<sup>4</sup> was able to collect 57 cases from the American literature. Only 24 of these were culturally proved cases. There was one brief report of a probable case from northern Wisconsin. An analysis of the cases revealed that the largest number from any single state was from North Dakota and that most of the cases occurred along the valley of the Missouri River.

Sutton<sup>5</sup> had previously reported a case, and within a year 11 cases had been reported from the Missouri Valley.

<sup>2</sup> Bull. Johns Hopkins Hosp., 1898, 9, 286.

<sup>3</sup> Sporotrichosis in Man, with Incidental Consideration of its Relation to Mycotic Lymphangitis in Horses, Jour. Cutan. Dis., July, 1910, 28, 321. (Complete bibliography to date, including the articles published during 1907 and 1908 in Bull. et mem. Soc. méd. d. hôp. de Paris.)

<sup>4</sup> Sporotrichosis in the United States, Jour. Infect. Dis., 1912, 11, 193.

<sup>5</sup> Sporotrichosis in the Mississippi Basin, *ibid.*, 1914, 63, 1153.



Haynes and Cheney reported the first case in West Virginia in 1914.

Blaisdell,<sup>6</sup> in 1917, reported the first case in New England. None have been reported since, although cases must have been seen since then,

The sporothrix has been found in every tissue of the body. The common type in this country is the localized lesion. Following an injury a nodule appears, often on the tip of a finger, ulcerates and discharges pus. Healing is very slow or does not occur. Within a short time a nodule forms along the lymph channels which drain the part and the lymph vessels become cord-like. Farther up another nodule forms, connected with the first by an indurated line of tissue slightly or not at all reddened. Others may form along the same line, so that a chain of several separate nodules may be seen along the arm or leg. They may ulcerate and cicatrize or become soft and break down with ulceration. Frequently if the nodules are close together the tissues are undermined and a probe may be passed in the subcutaneous tissue from one ulcer to another. As a rule there is not much tendency to spontaneous healing. The ulcers may last for weeks or months. The course is usually very slow. There are no disseminated gummatous lesions reported in this country.

In France especially there have been many widespread subcutaneous nodules and ulcerating forms reported. However widespread the lesions, they always begin as a firm, usually painless but sometimes very tender nodule in the subcutaneous tissue. In the disseminated form every nodule is separate and no cord-like tissue links it to its nearest fellow. After growing to a variable size the skin over the nodule becomes purplish, especially at the apex, and quite thinned, and fluctuation is felt. The nodule breaks, releasing a sanguinopurulent material. There is little or no zone of inflammation around the base of the nodule. The resulting ulcer has a punched-out appearance resembling so much a syphilitic ulcer that many errors in diagnosis have been made. The ulcer may show signs of healing, the base becomes clean and healthy granulations appear, while the epithelium grows in from the periphery. While some may be healing other nodules and ulcers are forming.

Although de Buermann and Gougerot stated, in 1907, that the regional lymphatic glands do not enlarge, this is not altogether true. They do not show the same tendency to become involved as do the glands draining tuberculous or syphilitic skin lesions, but they do enlarge and even become tender in many cases.

De Buermann and Gougerot, in 1907, reported the thirteenth case. This was an ascending gummatous lymphangitis located

<sup>6</sup> A Case of Sporotrichosis; First Case in New England, *Jour. Cutan. Dis.*, 1917, 35, 452.

on the arm of a man, aged fifty-seven years. It was the first case of the kind reported in France. A period of eighteen months elapsed between the appearance of the first and second abscess. In this case the axillary glands were not enlarged. That the course of the lymphangitis is not always as described above is shown by the case of Dominici and Rubens. The initial lesion was the result of a finger-cut. Later there were numerous scattered subcutaneous gummata on the arm without lymphangitis and without swelling of the lymph glands.

De Buermann and Gougerot saw a sporotrichal chancre of the forehead.

Alvin and Vallin<sup>7</sup> report a case of a large abscess and fistula in the brow of a woman, aged fifty-one years.

Daulos and Blanc report a case of palpebral sporotrichosis.

Wilder<sup>8</sup> reports conjunctival ulceration, culturally proved, in a laboratory assistant who was working with cultures of the sporothrix, and frequently capillary tubes were broken within ten inches of his eye.

Morax reports a most unusual case of uveal sporotrichosis with secondary episcleral lesions and absence of all other discoverable sporotrichal localizations.

De Buermann and Gougerot reported the first case of sporotrichosis of the pharyngeal mucous membrane. The organism was grown from the ulcer and also from the apparently intact mucous membrane.

Letulle and Klebré, in the course of a report on a case of sporotrichosis of the skin, mouth, pharynx, larynx and trachea in which the whole posterior buccal cavity was a shallow ulcer, say that the sporothrix buermanni can live an indefinite time in a saprophytic state.

Monier-Vinard and Gaucher, in 1907, reported the first case where the sporotrichum was grown from the sputum.

Widal and Weill reported, in 1908, a case of disseminated sporotrichosis with periosteal lesions in which the sporotrichum was recovered from the circulating blood. Widal and Abrami also showed at this time that the spores of the sporotrichum were agglutinated by the blood of patients affected with the disease in dilutions of 1 to 800. The blood serum of a patient with actinomyces agglutinated the sporotrichum in dilutions of 1 to 150. Complement fixation with the spores as antigen has also been described.

The disease usually begins as a local lesions at the site of some injury. The fact that the fungus lives as a saprophyte on all kinds of vegetables and dead matter and bark of trees makes it strange that the infections among humans are so few. Some curious

<sup>7</sup> Sporotrichosis, Lyon médical, October, 1920, 129, 859.

<sup>8</sup> Sporotrichosis of the Eye, Jour. Am. Med. Assn., 1914, 62, 11.

sources of infection have been reported. Thus, Sutton reports a case due to a hen-bite, Rouslacroix to a parrot-bite and others to bites of horses.

Olson<sup>9</sup> reported a case of the lymphangitic form in a man from North Dakota who had killed and handled many gophers, many of which had sores similar to those on the patient's hand. Many cases began from the crushing of a finger-tip and from cuts while in hay fields. Several cases are reported by the French of disseminated type in which no portal of entry could be found. The patients were vegetable venders and the organism was found on the vegetables.

Meyer<sup>10</sup> thinks that flies may act as passive carriers. In horses, dogs and rats in this country sporotrichosis is found spontaneously.

Davis<sup>11</sup> found that a small epidemic among horses on a farm in North Dakota which was thought to be farcy was sporotrichosis. The disease was also found among horses in Pennsylvania. Bovines do not seem to be susceptible to the disease but the hides may act as transmitters of spores (Meyer).<sup>12</sup>

All the American cases, with few exceptions, which I have been able to find have been of the lymphangitic type. A case reported by Ravogli,<sup>13</sup> in 1913, had a huge tuberculoid ulceration around an elbow.

Hyde and Davis's case was apparently the gummatous form. Le Blanc<sup>14</sup> has recently briefly recorded 2 cases of what had been thought to be pulmonary tuberculosis. He saw a small nodule on the larynx of each one and claimed that he found spores of sporotrichum in the sputum. There were no skin lesions.

Dominguez,<sup>15</sup> of Cuba, reported, in 1914, a case in a tobacco-leaf tester who was ill with fever and with the lung findings of pneumonia. His illness was prolonged and no tubercle bacilli could be found in the sputum. By roentgen-ray plate a shadow was found in the lung. A fungus lesion was then suspected and sporotrichum was grown from the sputum. Later an abscess of the middle ear developed from which sporotrichum was grown. An extradural abscess was operated and drained, but culture was negative for the fungus. The author found sporotrichum on the tobacco leaves.

Besides these lesions cases are reported by the French of genital lesions and muscle and bone lesions, and Councilman grew a sporotrichum from the fluid of a swollen and inflamed knee-joint.

<sup>9</sup> A Case of Sporotrichosis, *ibid.*, September 21, 1912, 59, 941.

<sup>10</sup> The Relation of Animal to Human Sporotrichosis, *Jour. Am. Med. Assn.*, 1915, 65, 579.

<sup>11</sup> *Loc. cit.*

<sup>12</sup> *Loc. cit.*

<sup>13</sup> Report of a Case of Sporotrichosis of the Tuberculoid Type, *Lancet-Clinic, Cincinnati*, 1913, 110, 112.

<sup>14</sup> Le Blanc, F.: Pulmonary Infection by Sporothrix of Schenck, *Ill. Med. Jour.*, December, 1920, 38, 516.

<sup>15</sup> Sporotrichosis with Multiple Localizations, *Med. Rec.*, April 4, 1914, 85, 603.

The case here reported is the only one of its kind recorded up to the present in the United States. The complete report of the bacteriologic, experimental and immunologic studies will be published later by my assistant, Arthur Margot.

**CASE HISTORY.** The case is that of a young negro, aged twenty-three years, admitted to the Milwaukee County Hospital March 8, 1920, who had followed the race horses as a stable boy in the southern and western circuits. He was born in Arkansas. Except for his journeys from New Orleans to California with the horses and a recent trip to Detroit he has always lived in the southern part of the country. He came to Milwaukee direct from Detroit and was in the city for five months before he was taken ill.

The family history is negative. As a boy he had measles, whooping-cough and mumps. When nineteen he had swollen and painful joints lasting a month, but was not confined to bed. At the age of fifteen he had both gonorrhea and an "eating chancre" without suppuration of the inguinal glands. He does not drink but smokes cigarettes to excess. He dated his present illness as far back as June, 1919, when he was ill with fever and chills, but was not confined to bed. Ever since then he has felt weak. About two weeks before admission a swelling appeared on the top of the right foot. There were no ulcerations of the toes, but the toes felt "sprung." This swelling was painful, at first hard, then later soft. It broke in about a week and yellow matter came out. It then began to heal. In the meantime nodules appeared on the top of the left foot, on both upper arms, posterior surfaces, both cheek bones and forehead. He became so weak that he entered the hospital.

Physical examination revealed a somewhat emaciated negro of medium height. On the left side of the forehead at the hair line was a soft painful swelling. There was slight dark discoloration of the skin of the nodule, and it was sharply demarcated from the surrounding skin. It measured 2 cm. in diameter and was raised about 1.5 cm. There was a rough bony edge encircling the base, as if the bone had been eroded. Behind the right ear was a tender superficial ulceration covered by a thin crust. The face was distorted by a swelling in the skin over each malar bone. One was somewhat softer than the other. On the exterior surfaces of both lower arms there were nodules, the largest measuring 3 cm. in diameter. All nodules were tender, some were discolored and others were not discolored. All showed more or less fluctuation. They appeared to be in the subcutaneous tissue. In the dorsum of the right foot there were three superficial ulcers, two of them almost healed; one measured 3 x 4 cm. and had a healthy granular base and a punched-out appearance.

There were moist rales at the bases of both lungs, more numerous

on the left side. The skin of the left posterior apex was very sensitive to palpation. The percussion note was slightly impaired and the breath sounds were a trifle harsh. No rales were heard. Over the whole left side the respiratory excursion was slightly limited and the tactile fremitus, percussion note and breath sounds were not as distinct as on the right side.

The heart was not enlarged; there were no murmurs; the rate was 90 to the minute; the pulse was soft and compressible.

The abdomen was retracted; no masses were felt; the liver and spleen were normal in size; the reflexes were normal.

There was irregular fever as high as 103° F. throughout the illness. The urine was normal at first, but later contained a slight amount of albumin, and shortly before death was full of bile pigments. The leukocytes were 17,000; the Wassermann reaction was + + + +.

As soon as he was seen by me he was thought to have an infection with some one of the fungus diseases. A soft nodule was aspirated under aseptic precautions and the yellow blood-stained pus was examined fresh and cultured. A mycelial network was found which on culture proved to be sporothrix.

Suspecting that there might be some lesion in the lung a roentgen-ray plate was made and the sputum examined. Nothing of interest was found in the sputum, which was scanty.

The roentgen-ray plate showed a clear right apex and slightly hazy left apex. There was a large, somewhat circular shadow extending from the right hilum, about 6 cm. in diameter. Radiating from the edge of this were fine linear markings extending into the first interspace and outward to the edge of the outer zone. Along the left heart border was some fine spotting. The left hilum was also increased in size.

In spite of large doses of potassium iodide and of arsphenamine new nodules developed at various places on the arms and legs while those on the face were gradually healing. Over the outer surfaces of both thighs very large undermined nodules developed. Cultures made from the contents of many nodules invariably showed the same sporothrix.

On April 1, it was noted that on the inner side of the middle of the left thigh was an elongated hard nodule from which a cord-like induration extended a short distance in both directions. Shortly after this he developed intense jaundice. One nodule over the left malar bone had increased in size; the skin was thin and bluish, but there was no elevation of temperature; 10 cc of a yellow purulent blood-stained fluid were aspirated from this nodule.

The patient gradually grew worse. Many nodules were open and were draining freely. The temperature was always elevated. He died on May 23, 1920.

It was not possible to autopsy the body until June 2, 1920, ten days after death. The report of Dr. Margot is as follows:

The body is that of a large-framed but extremely emaciated male negro. The legs and arms are swathed in bandages. Upon removal there are seen huge ulcerating surfaces with undermined discolored skin, one enormous cavity occupying a large part of the outer surface of the left thigh. At the scalp margin on the brow are two punched-out ulcerations. In the skin over the right malar bone is a fluctuating tumor 4 cm. in diameter and 2 cm. above the skin level. Over the left malar bone is a similar but larger nodule. The conjunctivæ have an icteric tint. The pupils are equal but rather large. Rigor mortis is present, postmortem lividity is marked. There is no edema.

*Thorax.* On removing the sternum the left lung lies entirely free from adhesions but shows a slight hypostatic congestion in the posterior portion of the lower lobe. There is an area of congestion on the posterior surface of the lower lobe of the right lung. A nodule about 1.5 cm. in diameter is found in the upper right lobe having the characteristics of those found in the skin. The mediastinum contains no enlarged glands.

*Heart.* The pericardium and heart reveal no abnormalities except for probable softening of the muscle.

*Abdomen.* The abdominal fat is scanty and has a yellow color. The peritoneal surfaces are smooth and glistening. No free fluid is found.

*Spleen.* The spleen is slightly enlarged; the surface is smooth; color dark; consistency irregular both soft and firm. On section there are dark-red dry areas which are firmer than the rest and extend deep into the spleen. The Malpighian bodies are pretty well seen throughout the cut surface.

*Liver.* The liver extends 4 cm. below the costal border. It is mottled and the external surface is smooth. It is firm. On section it drips blood. The cut surface is somewhat glistening and the cut edges roll over and the markings are indistinct.

*Kidneys.* The kidneys are slightly increased in size and are firm. The capsule strips readily from both. Typical cloudy-swelling markings are seen with a swollen cortex.

*Gall-Bladder.* The gall-bladder is distended and contains about 45 cc of purulent exudate and bile. The wall is thickened and edematous. No stones are found.

*Pancreas.* The pancreas appears not to be affected.

*Microscopic Examination of Tissues.* Owing to the fact that the body was ten days in the morgue before autopsy the tissues were more or less autolyzed. However, it was possible to obtain good specimens of the lung. Sections of the nodule in the right lung are made up of connective tissue in which are small round cells, scattered polymorphonuclear leukocytes, plasma cells and large

mononuclear cells, probably from the alveolar epithelium. The lung structure is completely obliterated. Many giant cells are present. These have irregular shapes; the protoplasm stains a uniform pink with eosin and the many apparently vesicular nuclei are arranged along the periphery of the cells, at times almost encircling the cell. The resemblance to the giant cells of tuberculous tissue is very close. There are lacking the caseous areas and the tubercle arrangement. There are many distended capillaries throughout.

The kidney sections show marked cloudy swelling with detritus in the collecting tubules. Many Bowman capsules are unusually thickened.

The liver sections show cloudy swelling and congestion of the central veins with atrophy of the liver cells for about one-third to one-fourth of the lobule.

No special changes are seen in the spleen or in a lymph gland at the hilum of the right lung.

Sections from the edge of several of the skin nodules show a connective-tissue stroma infiltrated with leukocytes, round cells and many giant cells much like those found in tuberculosis. Very few eosinophils were seen. Early stages of the nodules are made up of embryologic connective tissue infiltrated with many plasma cells and some polynuclear cells. As the nodule softens the leukocytes increase in number. No proliferation of capillaries is seen. Giant cells are found. It is often quite impossible in certain areas to differentiate these lesions from those of tuberculosis.

We grew the organism from the pus of several nodules on ordinary nutrient agar-agar in the incubator at room temperature. The best media were potato and Sabouraud's glucose peptone agar. At room temperature the growth is slow. In the incubator on agar at the end of twenty-four hours small circular colonies of silky-white appearance are seen and a dense branching, silken, whitish mycelium spreads over the surface. In tubes this penetrates vertically for a distance of 5 to 10 mm. into the depths of the medium. In addition to this adherent layer of interlacing filaments an abundant aerial woolly mass of filaments appears within forty-eight hours. Radiations of short filaments from the center of the growth on the agar surface are found from which fruiting hyphæ arise, at the free ends of which are sporangia. The columella, seen after the discharge of spores, projects in a spherical body from the funnel-shaped, expanding end of the supporting hyphæ. The spores are conical in shape; they are chlamydospores (Davis)<sup>16</sup> and measure about 4.5 micra in length, although the range is from 4 to 5 micra.

<sup>16</sup> Formation of Chlamydospores in *Sporothrix Schenckii*, Jour. Infect. Dis., November, 1914, 15.

After four to five weeks the growth on the agar or potato appears dry and the color changes from white to mouse gray on to dark brown. De Buermann, who described the first case in France five years after Schenck had published his report, has given his name to the organism, and possibly on account of his many publications the name of the sporotrichum is more widely known under the name *sporothrix buermannii* than under its correct name, *sporothrix schenckii*. Priority, however, in this case is undisputed and the organism should be known by its original name.

It would appear that de Buermann's organism and our organism are slightly different in their pathogenicity from the one described by Schenck and the ones described by Hektoen and Perkins, Hyde and Davis and others in this country. The difference lies in the ability of the first group to produce lung lesions in albino rats, whereas no lung lesions were ever produced by any of the previously described American sporotricha. Culturally there is no essential difference. Since Davis reported that the *sporothrix schenckii* produced chlamydospores, that distinction of the two species no longer served to differentiate them.

It is interesting that our case, the only one reported in this country which is similar to the gummatous cases reported in France, should be caused by a sporotrichum different in pathogenicity from all the reported American cases, but like that reported by the French investigators. We procured cultures from various parts of the country and injected them into rats. Our culture was the only one which produced lung lesions.

The spores alone develop and germinate in the organs of animals (Margot). An emulsion of spores was injected intravenously into rabbits, albino rats and guinea-pigs. Within ten to twelve days the animals developed cachexia, and if not killed died from the injection. Autopsy showed nodules scattered in the liver, kidney, spleen and brain. The nodules were subcapsular, deep, isolated and conglomerate. Cultures from the organs developed typical mycelium.

Only in the albino rats were lung lesions produced. Inoculation by any route invariably produced nodules in the lungs. The histologic appearance of the nodules was similar always, only varying in the proportion of giant cells and other formed elements. No spores were definitely found in the giant cells.

Our organism was agglutinated by the patient's blood (sporo-agglutination) in dilution of 1 to 150. Control sera gave no agglutination.

By using an emulsion of crushed spores as antigen, complement fixation was obtained. Unfortunately we neglected to draw blood from the living patient for culture. The result would have been interesting but of no value in diagnosis.



**Summary.** A case of disseminated gummatous sporotrichosis in a young colored man is reported. There was a nodule in the right lung, suspected on physical examination, seen in the roentgen-ray plate and confirmed at autopsy culturally and histologically. This is the first case of its kind reported in American literature. The sporotricha reported from American cases and some reported from French cases differ in the pathogenicity and in the ability to produce lung lesions in albino rats.

Attention is again called to sporotrichosis as a generalized disease and to the probability of cases of lung sporotrichosis which are unrecognized.

#### REFERENCES.

- Adamson, H. G.: A Résumé of the Literature Relating to Sporotrichal Infections of the Skin, *British Jour. Dermatol.*, 1908, 20, 296. (All literature to date.)  
 Hamburger, W. W.: Sporotrichosis, *Jour. Am. Med. Assn.*, November 2, 1912, 59, 1590.  
 Hamburger, W. W.: Sporotrichosis in the United States, *Ill. Med. Jour.*, February 1914, 25.  
 Quém, E.: (Sporotrichosis of the Breast), *Rev. de Chir.*, Paris, 1914, 34, 553-720.  
 Morax: (Uveal Sporotrichosis with Secondary Episcleral Sporotrichosis; Absence of All Other Discoverable Sporotrichal Localization), *Ann. d'occul.*, Paris, 1914, 152, 273.  
 Davis, B. F.: Report of a Case of Sporotrichosis, *Surg., Gynec. and Obst.*, 1914 19, 490.  
 Haynes and Cherry: Case of Sporotrichosis, First Case in West Virginia, *West Virginia Med. Jour.*, 1914-1915, 9, 303.  
 Wohl, M. G.: Report of a Case, *Nebraska State Med. Jour.*, December, 1920, 5, 355.  
 Brainos, A.: (Sporotrichosis of the Genital Organs), *Paris médical*, March, 1920, 10, 247.

---

### COMPARATIVE PROGNOSIS IN TUBERCULOUS LESIONS OF THE RIGHT AND LEFT LUNG. A STUDY OF 1048 CASES.

BY BARNET P. STIVELMAN, M.D.,

AND

NATHAN C. MILLER, M.D.

BEDFORD HILLS, N. Y.

(From the Montefiore Country Sanatorium, Bedford Hills, N. Y.)

VERY few, and somewhat conflicting, are the recorded observations on the comparative prognosis of right- and left-sided tuberculous lesions and bilateral lesions in which one lung is more extensively involved. Brown<sup>1</sup> maintains that there is no difference in gravity between lesions of the right and the left lung. On the other hand, other observers speak of the mildness of right-side lesions in comparison with those of the left side, and point to the

less favorable prognosis in lesions of the left lung. Text-books on the subject shed but little light on this phase of pulmonary tuberculosis, and references to such investigations cannot be found in most standard works on disease of the lungs. It is evident, therefore, that this subject will stand further investigation.

In reviewing the extensive literature on therapeutic pneumothorax one is impressed with the fact that the number of left lungs collapsed is far greater than that of the right, notwithstanding that, generally considered, the left lung is less frequently involved in pulmonary tuberculosis. This would indicate a greater frequency of severe lesions in the left lung. Impressed with this occurrence, Tecon and Aimard,<sup>2</sup> Mark<sup>3</sup> and others have carefully analyzed the data at their disposal. They conclude that as the disease advances there is a great preponderance of left-side lesions, and that a tuberculous condition in the left lung is of more serious import than one in the right and demands a more guarded prognosis. Mayer,<sup>4</sup> Cavalcanti,<sup>5</sup> Strandgaard<sup>6</sup> and others, although unable to confirm the above observation as regard the much greater frequency of left-lung involvements in the advanced stages of phthisis, agree, nevertheless, that the prognosis is less favorable in those whose predominating lesion is in the left lung.

The 1048 cases which form the basis of this communication were observed for from five months to several years. They were all subjected to repeated roentgenological examinations, and their diagnosis was clear cut. The classification of the National Tuberculosis Association was strictly adhered to, both in regard to diagnosis on admission and condition on discharge.

TABLE I.—LUNG INVOLVEMENTS IN 1048 CASES

Right lung only.	Left lung only.	Both lungs.	
		Right lung most.	Left lung most.
326, or 31.1 per cent	152, or 14.5 per cent	344, or 32.8 per cent	226, or 21.6 per cent

The figures of Table I show that of the 1048 cases studied, 152, or 14.5 per cent, suffered from tuberculosis of the left lung only and 226 from bilateral pulmonary tuberculosis with preponderating left-side involvement, or a total of 36.1 per cent of preponderating left-lung lesions; while 326, or 31.1 per cent, suffered from right-side lesions only, and 344, or 32.8 per cent, were afflicted with bilateral lesions in which the right side was more extensively involved; or a total of preponderating lesions of the right lung of 63.9 per cent. In other words, in unilateral lesions, the percentage of right-side involvement was about 2 to 1 as compared with

the left, while in bilateral lesions there was a decided increase in the number of involvements of the left lung, so that the percentage of preponderating right-side lesions was only 3 to 2 as compared with the left.

TABLE II.—LUNG INVOLVEMENTS IN THE VARIOUS STAGES OF PHTHISIS.

		Right.		Left.	
		No.	Per cent.	No.	Per cent.
Stage I	Male . . . . .	125	11.9	53	5.0
	Female . . . . .	70	6.7	44	4.2
Stage II	Male . . . . .	213	20.3	93	8.9
	Female . . . . .	115	11.1	60	5.8
Stage III	Male . . . . .	92	8.8	69	6.5
	Female . . . . .	55	5.1	59	5.7
Total . . . . .		670	63.9	378	36.1

Considering the various stages of the disease separately, Table II discloses the interesting fact that whereas in the first and second stage of the disease the percentage of the right-side lesions is about 2 to 1 as compared to the left side, the percentage of the right involvements in the third stage is not greater, but is about equal to that of the left. This is not in agreement with the figures of Tecon, Aimard and Mark, which show that in advanced phthisis the left side is much more often involved than the right. The evidence, however, points to a remarkable increase in the number of left-side lesions as the disease advanced.

TABLE III.—RELATION OF SIDE OF LESION TO ACTIVITY OF DISEASE.

	Male.				Female.			
	Right.		Left.		Right.		Left.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Inactive . . . . .	285	66.3	119	56.8	128	53.4	57	41.2
Active . . . . .	145	33.7	96	43.2	112	46.6	96	58.8

Analysis of Table III shows that both male and female patients in all stages of the disease whose preponderating lesion was on the left side ran an active course while at the sanatorium, more

frequently than those with preponderating right-side lesion, the ratio being 4 to 3 in favor of the left lung.

TABLE IV.—CONDITION ON DISCHARGE.

		Male.				Female.			
		Right.		Left.		Right.		Left.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Stage I	Arrested; improved . .	121	96.8	52	98.1	67	95.7	42	95.5
	Unimproved; progressive .	4	3.2	1	1.9	3	4.3	2	4.5
Stage II	Arrested; improved . .	176	87.4	80	86.0	95	82.6	48	80.0
	Unimproved; progressive .	37	12.6	13	14.0	20	17.4	12	20.0
Stage III	Arrested; improved . .	52	56.5	27	39.2	34	61.8	28	47.5
	Unimproved; progressive .	40	43.5	42	60.8	21	38.2	31	52.5
Total . . .		430		215		240		163	

Scrutiny of the figures in Table IV discloses the fact that in early tuberculosis the prognosis is no better in right than in left apical lesions. However as the disease advances the prognosis becomes less favorable in predominating lesions of the left lung. Thus the percentage of patients discharged "unimproved" and "progressive" in the second stage in male patients is 14 per cent in predominating left-lung lesions as against 12.6 per cent with right-lung involvements, and in the females 20 per cent "progressive" in lesions of the left lung as compared with 17.4 per cent in predominating right-lung lesions. In the third stage the prognosis in left-side lesions seems to be decidedly worse than in lesions of the right lung. Here the percentage of patients discharged with condition "progressive" is 60.8 per cent in left predominating lesions as compared with 43.5 per cent in right predominating lesions among the males and 52.5 per cent "progressive" in lesions of the left lung as compared with 38.2 per cent in right-side lesions among the females, or a ratio of 3 to 2 among males and 4 to 3 among females.

**Discussion.** Although it is universally admitted that the minimal lesion in pulmonary tuberculosis is most frequently found at the right apex the available data do not indicate the exact proportion of right and left apical involvements. This proportion varies within a wide range, depending on the character of the investigation. There is, however, a fair agreement that as the disease advances there is a decided increase in the number of left-lung

lesions, so that when we observe a group of patients in whom the disease has reached the so-called "third stage" we find that in cases with unilateral disease the left lung is involved as often as the right, and in cases with bilateral lesions the predominating lesion is discerned on the left side no less frequently than on the right. This in itself, however, does not shed much light on the relative prognosis in lesions of either side. When, on the other hand, we look into the results of institutional treatment in all stages of phthisis we gain a definite idea as to the relative prognosis of right- and left-side lesions. Our observations are in accord with most observers, to the effect that the prognosis in early right apical lesions is no better than in lesions of the left apex. It is quite different, however, in the advanced stages of phthisis. Here it is definite that the prognosis is less favorable in cases with predominating lesions of the left lung. These patients are liable to run an active course more often than those with preponderating right-side lesions, and the percentage of these cases discharged "unimproved" and "progressive" is almost one and one-half times as large as that of cases with right-side involvement.

There seems to be some conflict of opinion as to the probable explanation of the increased gravity in left-side lesions. It is stated that the narrow caliber of the left bronchus, by interfering with the proper aëration of the left lung, favors the rapid progress of the disease once it is implanted in its upper lobe. This explanation, however, does not seem to possess the germ of conviction.

A more rational explanation for the greater gravity in left-side lesions is to be found in this: The right lung has three lobes whereas the left lung has but two. The division of the lung into lobes seems to retard the rapid spread of tuberculosis because the fissures which separate the lobes are lined with double layers of serous membranes which are more refractory to tuberculous disease than the lung tissue proper. It is evident that the right lung with two fissures is better equipped to check the rapid spread of the disease than the left, which, after the one fissure is passed, has no other barrier to retard the spread of the disease.

It has recently been pointed out that even in health, areas of atelectasis are frequently found in the left lower lobe. These are probably caused by the encroachment of the pericardium and its contents on the left lower lobe and are responsible for the marginal rales which are so often heard in the region of the left base. Sewall<sup>7</sup> states that "a conclusion might be plausible that the atelectatic condition distinctly favors the development of phthisis." Is it not possible that, at least to some extent, atelectasis favors the rapid spread of tuberculosis in the left lung?

There are also causes which indirectly render the prognosis of lesions on the left side more serious. Clinicians have long recognized that patients suffering from phthisis stand the dislocation of the mediastinal organs to the right much better than their dis-

location to the left. Dyspnea, cyanosis, palpitation, etc., are not often complained of in acquired dextrocardia due to fibrosis and shrinkage of the right lung, whereas the above symptoms are often met with in a distressing form in patients with sinistracardia due to advanced tuberculosis of the left lung. We see many cases with extreme dextrocardia who work and do well generally for many years, but those whose cardiac displacement is to the left have but a small cardiac reserve and seldom do well.

Shrinkage of the left lung also causes marked retraction of the left diaphragm and adjacent abdominal viscera. In some instances the retraction is so extreme that the stomach is actually pulled into the thoracic cavity and simulates a diaphragmatic hernia or localized pneumothorax.<sup>8</sup> The normal function of the stomach is thus materially interfered with to a much greater extent than is possible in lesions of the right side, no matter how extensive. This further aggravates the prognosis in advanced disease of the left lung.

**Summary.** The results of our study lead us to conclude:

1. In early tuberculosis the right side is affected twice as often as the left.

2. As the disease progresses there is a marked increase in the number of involvements of the left lung, so that in the advanced stage of the disease the right and the left lungs are numerically equally involved.

3. Patients with a predominating left-lung involvement are liable to run an active course more often than those with preponderating right-side lesions.

4. In early phthisis the side of the lung involved has no definite relation to the general prognosis.

5. In advanced phthisis the prognosis is distinctly less favorable in those with preponderating lesions of the left lung.

6. The presence of but one interlobar fissure, moderate atelectasis and the evil effects of sinistracardia and retraction of the stomach are factors which contribute toward the greater gravity of left-lung lesions as compared to the right.

#### REFERENCES.

1. Modern Medicine (Osler and McCrae), Lea & Febiger, Philadelphia, 1915, 1, 461.
2. Gravité comparée des localisations tuberculeuses pulmonaires gauches et droites; Etude de 2000 cas, Rev. de la Suisse romande, January, 1917, 37, 45.
3. Comparative Prognosis of Tuberculous Lesions of the Right and Left Lung, Jour. Am. Med. Assn., May 10, 1919, 72, 1348.
4. Welche Lunge erkrankt am häufigsten an Tuberculose, München. med. Wchnsehr., August 6, 1920, 67, 935.
5. Ueber die Frage der Lokalisation des Lungentuberculose, Dissertation, Zurich, 1920.
6. Welche Lunge wird vorzugsweise durch Tuberkulose angegriffen, Ztschr., f. Tuberculose, 1910, 16, 114.
7. Pulmonary Atelectasis, Am. Rev. Tuberc., January, 1921, 4, 11, S11.
8. Stivelman, B.: False Pneumothorax, Jour. Am. Med. Assn., January, 1920, 74, 12.

# OBSERVATIONS ON THE BLOOD IN CASES OF CHRONIC NEPHRITIS ASSOCIATED WITH NITROGEN RETENTION.\*

BY BENJAMIN N. BERG, M.D.

NEW YORK.

(From the Medical Department of Mount Sinai Hospital, New York City.)

DURING the course of certain forms of chronic nephritis, anemia plays a prominent role in the clinical picture of the disease. Attempts have been made to correlate the anemia with the presence of edema, dilution of the blood being considered a possible explanation. Very early, von Jakseh<sup>1</sup> found that in chronic nephritis edema held no constant relation to the plasma content of the blood. The studies of Keith, Rowntree and Geraghty,<sup>2</sup> and more recently those of Bock,<sup>3</sup> seem to indicate that in chronic nephritis, as well as in other conditions, the plasma volume of the blood remains remarkably constant, variations in total blood volume being due to the corpuscular content. Edema does not affect the plasma volume to any appreciable extent. Ewing<sup>4</sup> found that severe anemia occurs in chronic nephritis, especially in cases associated with edema; but he also observed cases of severe anemia in nephritics without edema. With the introduction of more accurate methods of determining the constituents of the blood serum, and especially the nitrogen partition, Widal, Abrami and Brule<sup>5</sup> reported a case of severe anemia occurring in a nephritic without edema, but with nitrogen retention. Recently, Aubertin and Yacoel<sup>6</sup> reported two cases of chronic nephritis, with nitrogen retention, in which a severe anemia was present, making the added observation that anemia was relatively rare among cases of the non-nitrogen retention type. They collected a series of cases which demonstrated that the anemia was practically exclusively encountered in cases of chronic nephritis showing nitrogen retention and no edema.

Through the courtesy of Drs. Brill and Libman, I was enabled to study the following cases in detail:

CASE I.—Mrs. I. M., aged forty-six years, married, Austrian, housewife, was admitted September 21, 1920, complaining for

\* Read before the Section on Medicine at the New York Academy of Medicine, May 17, 1921.

<sup>1</sup> *Ztschr. f. klin. Med.*, 1893, 23, 187.

<sup>2</sup> *Arch. Int. Med.*, October, 1915, 16, 547.

<sup>3</sup> *Ibid.*, January, 1921, 27, 83.

<sup>4</sup> *Clinical Pathology of the Blood*, 1903, p. 414.

<sup>5</sup> *Bull. et mém. Soc. med. des hôp. de Paris*, 1907, p. 1427.

<sup>6</sup> *Presse méd.*, 1920, 28, 461.

three years of headaches, general weakness and yellowish discoloration of the skin. She had a history of "kidney trouble" fifteen years before; at that time she was ill for four months. Edema was present. Eleven years ago she had a miscarriage. The menopause occurred three years ago.

Her present illness began three years ago, with intermittent headaches of a thumping nature, most severe over the parietal and occipital regions, and radiating down to the back of the neck. Attacks of headache began suddenly, lasted twenty-four hours or longer and gradually subsided. During the attack the patient vomited, often ten to twelve times; the vomiting was not projectile. There were recurrences nearly every week. For the last three weeks the headaches have become constant but less severe; the attacks of vomiting have become less frequent.

The patient has had frequent attacks of epistaxis during the last three years. She complains of marked weakness. Her vision has been poor for the last three years. There have been no convulsions or paralyses. Three years ago she noticed that her skin was becoming progressively yellow. Her appetite has been poor; she has been habitually constipated. Her stools have never been clay colored or tarry. Hematemesis occurred on two occasions several weeks ago. Micturition four or five times daily, moderate amounts; nocturia three or four times. There has been no edema of the face or extremities. She has lost sixty pounds within the past three years. Cardiac and respiratory symptoms have been absent.

**Summary:** "Kidney trouble," associated with edema, fifteen years ago; a miscarriage eleven years ago; for three years had headaches associated with vomiting, weakness, yellow skin, epistaxis and blurred vision; hematemesis several weeks ago; nocturia; loss of sixty pounds in weight within the last three years.

**Physical Examination:** The physical examination showed a poorly-nourished, fairly well-developed woman of middle age. Her skin had a waxy yellow appearance; the conjunctivæ and other mucous membranes showed marked pallor. All the teeth were missing. There was marked distention of the jugular veins and marked episternal and supraclavicular arterial pulsations. The lungs were negative. The heart borders were not enlarged, the sounds were of fair quality; there was a soft, blowing systolic murmur at the apex, which was transmitted toward the axilla. The radial pulses were regular and equal, of moderate rate, fair force and volume; the arterial walls were thickened and tortuous. The abdomen was negative. The extremities showed no edema; the reflexes were active and equal. Over the skin of the extremities were scattered ecchymoses; there were a few petechiæ over the left breast. The cervical lymph nodes were enlarged. Vaginal and rectal examinations were negative.



Upon admission the patient's systolic blood-pressure was 235, and the diastolic 120. The urine showed a moderate amount of albumin, with a specific gravity of 1006; there were present a few epithelial cells and leukocytes. The urinary output in twenty-four hours was 600 cc. The phenolsulphonephthalein test showed less than 5 per cent excretion in two hours.

Blood Examination. September 22, 1920:

Hemoglobin, 55 per cent (Kuttner).

Erythrocytes, 2,500,000.

Hemoglobin index, 1+.

Leukocytes, 4800.

Polynuclear neutrophiles, 76 per cent.

Lymphocytes, 13 per cent.

Monocytes, 11 per cent.

Smear. Erythrocytes fairly well filled. Slight anisocytosis and poikilocytosis. No macrocytes or normoblasts seen.

Coagulation time: 8 minutes.

Blceding time:  $2\frac{1}{2}$  minutes.

Fragility test: Hemolysis begins at 0.375; complete at 0.30.

Capillary resistance, hemostaxis appears in 5 minutes.

Blood Examination. September 24, 1920:

Hemoglobin, 42 per cent (Kuttner).

Erythrocytes, 2,120,000.

Hemoglobin index, 1.

Leukocytes, 4800.

Polynuclear neutrophiles, 75 per cent.

Lymphocytes, 22 per cent.

Monocytes, 3 per cent.

Smear: Erythrocytes of good shape and color. Occasional polychromatophilic macrocytes and stippled erythrocytes seen.

Two further blood determinations gave practically the same findings as the last.

Blood Chemistry. September 23, 1920:

Urea nitrogen, 54.6 mg. per 100 cc.

Incoagulable nitrogen, 126.0 mg. per 100 cc.

Uric acid, 7.2 mg. per 100 cc.

Creatinin, 4.6 mg. per 100 cc.

Cholesterin, 0.212 per cent.

Blood Chemistry. October 18, 1920:

Urea nitrogen, 123.2 mg. per 100 cc.

Incoagulable nitrogen, 180.0 mg. per 100 cc.

Uric acid, 8.5 mg. per 100 cc.

Creatinin, 11.0 mg. per 100 cc.

Cholesterin, 0.108 per cent.

The urine continued to show a moderate amount of albumin. The specific gravity varied from 1006 to 1009. The urinary output in twenty-four hours averaged one liter. The systolic blood-pressure fell to 170 and the diastolic to 100. The Wassermann reaction was negative. The Rehfuss test after the first hour showed complete absence of free hydrochloric acid; the total acidity was 20.

With the aid of colonic irrigations, forced fluids and medication she became more comfortable. After a six weeks' stay in the hospital she left against advice. The figures for the blood chemistry indicated a poor prognosis.

**CASE II.**—Miss Y. R., aged twenty-six years, a Roumanian, milliner by trade, was admitted February 7, 1921, complaining for six weeks of pain in the back and right side, progressive weakness and edema of the face. The family and personal histories were negative. During childhood she had measles, whooping-cough, scarlet fever and diphtheria. Eight years ago she had suffered from swelling of the face, abdomen and extremities, which gradually improved in the course of one and a half years. Three years ago she had typhoid fever. She also had influenza about that time. The patient has had occasional attacks of palpitation and dyspnea upon exertion. Attacks of sore-throat had been frequent. The menstruation had always been normal.

The present illness began six weeks before admission, with an attack of vomiting and fever, associated with pain in the right side and back. The pain was sticking in character, radiating down to the legs and up to the shoulder. It was so severe at times that it kept the patient awake at night. She claims to have noticed swelling of the face. Weakness and malaise have been very marked since the onset of her present symptoms. She has had frequent headaches, and experiences a dizzy feeling when standing. There have been palpitation and dyspnea upon exertion, associated with moderate precordial distress. She has not vomited since the original attack. Nocturia has been marked.

**Summary:** Infectious diseases of childhood; swelling of the face, abdomen and extremities eight years ago; typhoid and influenza three years ago; palpitation and dyspnea; pain in the back, weakness and edema of the face (?) for the last six weeks; headaches and dizziness; nocturia.

**Physical Examination:** The patient was a fairly well-developed and well-nourished young woman who appeared to be chronically ill. The conjunctivæ and other mucous membranes were very pale. The following were the positive findings: The facies was suggestive of myxedema rather than of a true edema of the face; the skin was somewhat thickened and had a yellowish pallor. The heart was moderately enlarged. At the apex the first heart

sound was replaced by a prolonged, soft, blowing murmur, systolic in time, transmitted toward the axilla and heard over the entire precordium. The second heart sound was of fair quality and intensity. The aortic second was louder than the pulmonic second. The radial pulses were equal, regular and of moderate tension; the arterial walls were not thickened. The lungs were negative. The abdomen was negative except for slight tenderness in the right upper quadrant. There was no edema of the extremities.

Upon admission the patient's systolic blood-pressure was 170 and the diastolic 120. The urine contained a large amount of albumin with a specific gravity of 1008; a few leukocytes were present. The urinary output in twenty-four hours was one liter. The phenolsulphonephthalein test showed no dye excretion in two hours.

Blood Examination. February 8, 1921:

Hemoglobin, 31 per cent (Kuttner).

Erythrocytes, 1,500,000.

Hemoglobin index, 1+.

Leukocytes, 5400.

Polynuclears neutrophiles, 65 per cent.

Lymphocytes, 33 per cent.

Monocytes, 2 per cent.

Smear: Erythrocytes show slight anisocytosis and poikilocytosis.

Blood Examination. February 13, 1921:

Hemoglobin, 33 per cent (Kuttner).

Erythrocytes, 1,504,000.

Hemoglobin index, 1+.

Leukocytes, 6600.

Polynuclears neutrophiles, 71 per cent.

Lymphocytes, 25 per cent.

Monocytes, 4 per cent.

Smear: Erythrocytes show slight anisocytosis and poikilocytosis.

Fragility test: Complete hemolysis, 0.200 to 0.250; partial hemolysis, 0.275 to 0.425; no hemolysis, 0.450 to 0.625.

Further blood determinations showed a progressive anemia.

Blood Examination. March 10, 1921: (The patient had frequent but slight epistaxis at this time):

Hemoglobin, 22 per cent (Kuttner).

Erythrocytes, 1,252,000.

March 15, 1921:

Hemoglobin, 20 per cent (Kuttner).

Erythrocytes, 1,120,000.

Coagulation time,  $7\frac{1}{2}$  minutes.

Bleeding time, 11 minutes.

Blood negative for bile and urobilin.

May 12, 1921:

Hemoglobin, 22 per cent (Kuttner).

Erythrocytes, 1,040,000.

Blood Chemistry. February 8, 1921:

Urea nitrogen, 50.4 mg. per 100 cc.

Incoagulable nitrogen, 104.2 mg. per 100 cc.

Uric acid, 6.9 mg. per 100 cc.

Creatinin, 6.0 mg. per 100 cc.

Cholesterin, 0.276 per cent.

Blood Chemistry. March 4, 1921:

Urea nitrogen, 53.2 mg. per 100 cc.

Incoagulable nitrogen, 116.7 mg. per 100 cc.

Uric acid, 4.1 mg. per 100 cc.

Creatinin, 8.5 mg. per 100 cc.

The urine continued to show a large amount of albumin. The specific gravity varied from 1004 to 1012. The urinary output in twenty-four hours averaged 1300 cc. The systolic blood-pressure dropped to 120 and the diastolic to 80. The stool gave a positive reaction to the guaiac test, and on two occasions contained *ascaris lumbricoides*.

The therapy consisted of the following: Forced fluids and the Murphy drip, the Karrel diet, colonic irrigations with sodium bicarbonate and hot packs.

When the patient's hemoglobin fell to 20 per cent a citrate transfusion of 500 cc was performed (April 12). Clinically she benefited markedly, her hemoglobin rising to 32 per cent. This was of short duration, however, the hemoglobin rapidly falling to 22 per cent. Her condition is growing progressively worse.

Similar to the cases reported by Aubertin and Widai these patients present two syndromes: First, a severe anemia characterized by a high hemoglobin index, relatively little change in the morphology of the erythrocytes, absence of abnormal forms in the blood and a leukopenia, and second, a chronic nephritis with high nitrogen figures and uremic symptoms.

The following data were collected to determine:

1. The relative frequency of anemia in chronic nephritis, with and without nitrogen retention.
2. Whether there was any relation between the presence of edema and the occurrence of anemia.
3. The characteristics of the anemia.
4. The etiology of the anemia.

## CASES OF CHRONIC NEPHRITIS WITH NITROGEN RETENTION

Case No	Edema	Urea nitrogen	Erythrocytes	Hemoglobin, per cent	Hemoglobin index	Leukocytes
I. . .	0	54 6 123 2	2,500,000 2,120,000	55 42	1.1 1 0	4,800 4,800
II. . .	+	50 4 57 2	1,544,000 1,504,000	31 33	1 0+ 1 0+	5,400
III. . .	+	49 0	2,228,000	50	1 1+	9,000
IV. . .	0	121 8 126 0	4,180,000 2,900,000	73 65	0 8+ 1 1+	
V. . .	Slight	43 4 68 0	2,650,000	55	1 0+	8,000
VI. . .	+	107 8	2,520,000	45	0 9	
VII. . .	Slight	78 0	2,480,000 2,064,000	42 32	0 8+ 0 8	12,000 14,200
VIII. . .	Slight	54 6	2,500,000	40	0 8	7,400
IX. . .	0	71 4	2,824,000	43	0 7+	6,200
X. . .	0	154 0 214 2	2,300,000	40	0 8+	20,000
XI. . .	0	156 8	3,200,000	45	0 7+	8,200
XII. . .	0	140 0	3,300,000	58	0 9	14,000

## CASES OF CHRONIC NEPHRITIS WITHOUT NITROGEN RETENTION

Case No	Edema	Urea nitrogen	Erythrocytes	Hemoglobin, per cent	Hemoglobin index	Leukocytes
I.	0	18 2	5,000,000	80	0 8	8,400
II. . .	0	12 6	4,800,000	86	0 9	12,800
III. . .	+	21 0	4,800,000	94	0 9+	8,800
IV. . .	0	11 2	4,860,000	75	0 7+	9,400
V. . .	+	15 4	4,520,000	86	0 9+	5,300
VI. . .	+	18 2	4,480,000	80	0 9+	8,000
VII. . .	+	26 6	4,200,000	81	0 9+	13,000
VIII. . .	+	22 4	4,000,000	70	0 8+	18,000
IX. . .	0	28 0	4,000,000	77	0 9+	7,200
X. . .	+	25 2	4,000,000	70	0 8+	6,000
XI. . .	0	23 8	4,565,000	82	0 9	
XII. . .	+	21 0	5,000,000	90	0 9	
XIII. . .	+	12 6	3,500,000	64	0 9+	7,200
XIV. . .	-	14 0	3,480,000	84	1 2+	8,300
XV. . .	+	12 6	3,500,000	64	0 9+	7,200
XVI. . .	+	14.0	3,000,000 2,910,000	45 42	0 7+ 0 7+	5,000

**Summary:** As far as possible, those cases were chosen in which one could be reasonably certain that the anemia was not secondary to some complication such as hemorrhage, parasitic infection or new growth.

A study of these cases indicates that severe anemias occur nearly exclusively in chronic nephritis associated with nitrogen retention. Cases XI and XII in this group show relatively less advanced anemias. Only single blood counts, however, were made, and

the cases were not followed up. In the non-nitrogen group, Case XVI, which shows a severe anemia with low nitrogen figures, was in an advanced condition of cachexia upon admission; the anemia was probably associated with the nutritional disturbance. There is undoubtedly a large number of cases like XIII, XIV and XV which do not fit in either group. These cases may be in a phase of transition. Though the nitrogen figures have not increased there is present a moderate anemia. In such cases the anemia may be the precursor of changes in the figures for blood chemistry.

It is of interest to note Cabot's<sup>7</sup> statement that in chronic nephritis (without regard to the presence or absence of nitrogen retention) anemia is a relatively infrequent finding. In a study of 64 cases he found only 12 with an erythrocyte count of two to three millions and only three with a count between one and two millions. In our series of cases the relative frequency of anemia in all types of chronic nephritis coincided, approximately, with Cabot's figures. It should be added that the erythrocyte counts in our cases did not reach the low levels reported by Cabot and Aubertin.

Edema holds no constant relation to the presence or absence of anemia. According to our statistics anemia may exist in the absence of edema, and edema may occur without an associated anemia.

The most striking feature of the anemia in the nitrogen retention group is the high hemoglobin index. In many of the cases reported in this group (I to V inclusive) the hemoglobin index is above 1; the remainder of the cases also show a relatively high index. Among the more important conditions in which a hemoglobin index over 1 is found are the following: Primary pernicious anemia, bothrioccephalus infection, pernicious vomiting of pregnancy and new growths, especially bone tumors with metastases. Ewing<sup>8</sup> notes the fact that a high hemoglobin index occurs in the anemia of chronic nephritis. He adds that "grave or pernicious anemia develops in a small proportion of cases of chronic parenchymatous nephritis and appears, at times, to result directly from the nephritis." Blood smears in cases of chronic nephritis with nitrogen retention and a severe anemia, studied by us, were usually negative for the abnormal forms found in pernicious anemia. However a few polychromatophilic macrocytes were found in a case studied by Dr. N. Rosenthal. Further studies are needed on this point.\* The erythrocytes were usually well preserved and well filled with hemoglobin; macrocytes and normoblasts were not found. The leukocytes showed no marked changes either in number or character. In Cases I and II a leukopenia was present; Cases VII, X and XII presented a leukocytosis. The

<sup>7</sup> Clinical Examination of the Blood, 1904, p. 365.

<sup>8</sup> Loc. cit.

\* Many macrocytes were found in a case which was studied very recently.

differential count, except for a slight polynucleosis, was not abnormal. Myeloblasts, myelocytes and lymphoblasts were not noted. The blood picture presented by these cases is not uncommonly found in such conditions as carcinomatosis accompanied by severe anemia; in the latter form, however, abnormal erythrocytes or leukocytes, or both, are liable to be present.

It is of interest to note briefly the observations made by Aubertin and others with respect to the bone-marrow reactions in severe anemias occurring in chronic nephritis with nitrogen retention. Aubertin and Yacoel<sup>9</sup> report two cases, in which the blood pictures closely resemble those studied in our series; subsequent study of the bone-marrow, made by these investigators, revealed it to be macroscopically very fatty, and microscopically there was no evidence of activity. Elsewhere, Aubertin<sup>10</sup> reports a case of latent interstitial nephritis in which eclampsia developed. The blood picture was that found in pernicious anemia, there being present a high hemoglobin index, macrocytes, normoblasts, polychromatophilia, myelocytes and a relative lymphocytosis. The bone-marrow in this case was hyperplastic. On the other hand, Widal<sup>11</sup> reports a case of chronic nephritis with nitrogen retention in which the blood picture showed a very severe anemia with a hemoglobin index above 1. The blood smear showed complete absence of myeloid reaction.

The nature of the anemia in chronic nephritis with nitrogen retention, therefore, cannot be determined from the blood picture alone. Studies of the bone-marrow and spleen are necessary properly to interpret the anemia. Studies made thus far seem to suggest that the hematopoietic organs are profoundly affected in this form of nephritis.

As far as an etiologic factor is concerned nothing can be determined until more is known about the etiology of uremia. The anemia might be due to a hemolytic agent acting directly upon the erythrocytes; it might also be due to an inhibitory action by the same agent or some other unknown toxic factor upon the hematopoietic organs; a combination of both factors would possibly be responsible.

We expect to undertake investigations directed toward determining more accurately the reaction of the bone-marrow and spleen in cases of chronic nephritis associated with nitrogen retention and accompanied by a severe anemia.

**Conclusions:** 1. Severe anemia in chronic nephritis occurs principally in cases accompanied by nitrogen retention.

2. The anemia is characterized by a high hemoglobin index, often over 1, with relatively slight morphologic changes in the

<sup>9</sup> Loc. cit.

<sup>10</sup> Thèses de Paris, 1905, p. 135.

<sup>11</sup> Loc. cit.

erythrocytes. It therefore constitutes an additional form of anemia of the hyperchromic type.

3. Edema bears no constant relation to the presence or absence of the anemia.

4. The character of the anemia suggests profound alterations in the activity of the hematopoietic organs.

## THE PRESENT STATUS OF THE TREATMENT OF HAY FEVER AND ASTHMA.\*

BY A. VANDER VEER, JR., M.D.,  
NEW YORK.

(From the Department of Bacteriology and Immunology, Division of Immunology, Cornell Medical School, First Medical Division, New York Hospital.)

THE observations, statistics and conclusions set forth in this paper are founded on about 2000 case histories of asthma, hay fever and allied conditions treated during the past four years. An attempt has been made to determine, as accurately as possible, such advances in the modern treatment of these conditions as are due to the recent discoveries in the field of allergy, or human hypersensitiveness.

For more than ten years we have been treating hay fever by injections of pollen extract<sup>1</sup> and now have sufficient data to judge whether it is advisable to continue such treatment. At the end of each season a questionnaire is sent to the hay fever patients, which they are requested to fill out and return, checking the class to which they think they belong. Class A means that the hay fever has been entirely relieved, Class B greatly diminished, Class C diminished, but to a slight extent, and Class D, hay fever as bad as ever. The following table shows the number of answers returned each year with the percentage in each class for the last four years:

Year.	Number of answers.	Class A, per cent.	Class B, per cent.	Class C, per cent.	Class D, per cent.
1917 . . . . .	379	20	52	18	10
1918 . . . . .	400	25	51	15	9
1919 . . . . .	473	25	49	17	9
1920 . . . . .	522	20	44	24	12
Total . . . . .	1744	23	49	18	10

Roughly we may say 25 per cent are entirely relieved, 50 per cent are quite comfortable, 15 per cent are slightly relieved and 10 per cent are not helped. In other words, 75 per cent of the

\* Read before the Scranton Medical Society, March 1, 1921.

<sup>1</sup> For full details of such treatment see R. A. Cooke, Medical Clinics of North America, November, 1917, No. 3, 1.



patients can go about their business suffering very little discomfort. This is a great improvement over the time when a patient had but two alternatives—a trip to the White Mountains or Europe during the season of their disability, or else local nasal treatment either by sprays or operation, which nevertheless fails in the majority of cases.

The results of treatment vary somewhat according to the severity of the season, the strength of the extract used and the intelligence of the patient. All of these factors can and will be modified for the better as time goes on. Cities will make provision for the destruction of ragweed before it has a chance to pollenize, patients will learn more of the principles of the treatment and give valuable aid in the graduation of their doses, and finally it now seems as if the greatest difficulty of all, preserving the proper strength of the extract, has been overcome. Heretofore we have been unable to make an extract which would retain its strength for more than two or three months, but within the last year we have obtained one which has kept practically stable for over six months, long enough to last from the beginning of treatment through the season without changing from one extract to another.<sup>2</sup>

At present I do not think we can hold out to our patients the hope of permanent immunity. Occasionally a case is apparently cured by one or more years' treatment, but these cases are prone to relapse, and it is safer to advise treatment each year. Fortunately there is a natural tendency to outgrow the hypersensitiveness, and we have a number of cases on record of spontaneous cure, so that it is well to protect the patient by injections until such a happy result occurs. Even if a case does badly the first year it is well to persevere with the treatment, as there is frequently improvement during the succeeding years. Patients cannot become more sensitive by the injections, and the majority of the failures are due to too small doses or to inability to discover and use the particular pollen to which the case is hypersensitive.

When should we advise operative procedure on the nose? If there is obstruction all the year around, that is manifestly due to a pathologic condition and not to an allergic reaction to something besides pollen (as dust, sachet, chicken epithelium), this can probably be improved by operation, and this will, of itself, lessen the severity of the hay fever; but if the nose is perfectly clear except during the season we have found that operation is not advisable and will be of no benefit to the patient. On general principles, operations should not be performed during the pollen season, as the reaction from the trauma to the already inflamed mucous membrane will greatly increase the discomfort.

<sup>2</sup> Full details of the preparation of such an extract will shortly be published by Dr. Arthur F. Coca, of the Department of Bacteriology and Immunology, Division of Immunology, Cornell Medical School.

The disadvantages to the pollen injections are negligible with one exception, and that is the danger of an overdose causing a constitutional reaction. This may occur in from 1 to 2 per cent of all injections and takes the form of a sudden general urticaria or an acute attack of asthma or hayfever. The reaction manifests itself in from five to thirty minutes after the injection and can be promptly controlled by one or more injections of epinephrin (1 to 1000 solution) hypodermically. An initial dose of 6 to 10 minims is used, and this can be repeated in ten minutes if necessary. A third dose is almost never required, and there is no disadvantage in the use of the epinephrin except a nervous, shaky, chilly feeling when more is given than is necessary. This passes off within fifteen to twenty minutes. After a constitutional reaction the next dose of the pollen extract should be decreased slightly and then gradually increased again. With our more stable extract we are working out a system of increases which will practically eliminate the danger of constitutional reactions.

Injections are given every five to seven days, which take but a moment and give very little local reaction except a slight swelling, soreness and itching of the arm. The maximum dose should be reached before the season starts, and should be repeated every five to ten days during the season, as the immunity derived from each injection lasts but a week or so and then rapidly begins to diminish.

We usually employ an extract from a single pollen—timothy for the early cases and ragweed for the late, as the largest percentage of all the trouble comes from these two, either because of their greater prevalence or their greater activity. The cases unrelieved or only partially relieved by a single pollen extract should receive in addition extracts of other pollens to which they are found to be sensitive.

In addition to the pollen injections other measurers are of value in relieving the patient's discomfort. During an acute attack a thorough cleansing of the nose with a dilute solution of adrenalin and cocain will give better drainage and a similar solution in the eyes allays the itching and burning. It is wise to avoid excessive exposure, and if it is necessary to take a long automobile ride through the country on a dusty road it is well to wear goggles to protect the eyes, as much of the pollen is conveyed to the nose by way of the nasal duct. Atropin tablets,  $\frac{1}{200}$  to  $\frac{1}{150}$  grain, will dry up excessive nasal secretion and relieve slight attacks of asthma. For a severe attack of asthma it is necessary, of course, to give epinephrin hypodermically in 6 to 10 minim doses, repeated as occasion may require. Do not give morphine. Its immediate effect is inferior to the epinephrin, it has unpleasant after-effects and there is always the danger of forming a habit. Patients are often more comfortable if they sleep propped up in bed and with

the windows closed. Ragweed should be eradicated from the immediate neighborhood as far as possible.

Let us now take up the more difficult but fascinating study of asthma. The best definition and classification is that given by Cooke:<sup>3</sup>

Bronchial asthma is a condition characterized by dyspnea, both inspiratory and expiratory, due to edema of the bronchial mucous membrane and possibly to bronchial spasm. It may be acute, subacute or chronic. The term *bronchial asthma* should be restricted to that condition which is the result of an allergic action.

#### CLASSIFICATION.

1. Allergic . . .	(a) By inhalation	{ Animal dander. Pollens. Sachets and perfumes.
	(b) By ingestion.	{ Drugs. Foods.
	(c) By absorption from focus	{ Bacterial proteins (very questionable).
	(d) By subcutaneous or intravenous injection	{ Therapeutic sera.
2. Non-allergic . . .	Acute bronchitis.	
	Chronic bronchitis and emphysema.	
	Pulmonary tuberculosis.	
	Cardiorenal disease.	
	Thymic enlargement.	
	Enlarged bronchial glands.	
	Reflex bronchial spasm.	

In diagnosing a case of asthma our chief reliance in finding out the source of the trouble (after a careful history has been taken) is the skin test. This is founded on the discovery that usually the skin of an allergic subject manifests the same hypersensitiveness as the nasal and bronchial mucous membranes, and if an extract of a foreign substance to which the patient is hypersensitive is introduced into the skin a characteristic urticarial wheal will result. There are two common methods now in vogue of performing such skin tests: The intradermal and the dermal or scratch method. In the first a minute quantity ( $\frac{1}{100}$  cc) of a fluid extract is injected into the layers of the skin by means of a fine hypodermic needle. In the second the skin is incised with a sharp scalpel, not deeply enough to draw blood; the dry substance is placed on the incision and a drop of  $\frac{N}{10}$  sodium hydrate is added to dissolve the substance and bring it into contact with the skin. We have used both methods and find they each have their advantages and disadvantages. The intradermal method is easier to handle, is quicker and more delicate. Its disadvantage is that it is more liable to cause a constitutional reaction, due to the fact that it is

<sup>3</sup> Tice's System of Medicine (in press).

more delicate. While these constitutional reactions are rare they are sufficiently unpleasant when they do occur to demand every safeguard one can employ against them. They are exactly like those caused by an overdose of pollen extract and are controlled by an injection of epinephrin. They occur most frequently when testing with horse serum (in a 1 to 10 dilution), horse epithelium and egg-white. With the scratch method constitutional reactions are less liable to occur, but at the same time one is liable to miss many reactions which are perfectly plain and decisive with the intradermal method.<sup>4</sup>

The accuracy of the skin tests varies according to the substance used. With pollen, animal epithelia and sachet extracts they are extremely accurate in proper dilution. That is, they give corresponding reactions almost invariably at any time they are tried on the same subject, and are almost always indicative of being a causative factor in the patient's trouble.

The food tests are much less reliable, as the following table will show.

	Positive history, positive reaction.	Negative history, negative reaction.	Positive history, negative reaction.	Negative history, positive reaction.	Reaction and history correspond per cent.	Reaction and history do not correspond per cent.
Pollen cases . . .	155	29	4	4	96	4
Animal epithelia . cases . . . . .	20	17	2	0	95	5
Food extract cases .	9	6	11	3	50	50

Thus with the food reactions we are less certain of our ground. They often give different reactions at different times (and we have not been able to determine that this is due to the patients' having recently eaten or abstained from such food,) and we often find instances in which the skin reaction does not agree with the clinical history at all; that is, patients may eat with impunity foods giving positive skin reactions or may have very definite trouble from foods giving a negative reaction. It is easy to see why this should be so. Pollens, animal epithelia and other inhalants come unchanged in direct contact with the hypersensitive mucous membrane and produce their effects almost at once. Foods introduced into the gastro-intestinal canal are broken down into other split products, then absorbed and brought into contact with the hypersensitive membranes in a quite different form from the original food and may produce their effects hours or days after their ingestion. Eventually we will know more of these split products and their delayed or negative reactions will then be explained.

Skin reactions to milk and eggs occurring in children hypersensitive to such foods seem to be more reliable than other food test in adults. This hypersensitiveness they almost invariably

<sup>4</sup> Dr. Aaron Brown, in a paper to be published shortly, will give in detail the experiments on which these conclusions are founded.

outgrow in later life. We are convinced that the role of foods as a causative factor in the production of asthma has been greatly overestimated in the past, and that the great majority of cases are due to some inhalant. This conviction is based on the fact that it is usually impossible to induce an attack of asthma by the ingestion of foods giving positive reactions, that patients are often free of asthma for long periods of time while still eating such foods, and conversely often continue to have asthma even though abstaining from such foods.

The following table will give an idea of the relative frequency of the various causes of asthma, comparing 135 cases treated in 1917 and 122 cases treated in the first six months of 1920. This table excludes patients seen only once or twice and comprises those in whom it was felt a diagnosis should have been made. They are listed under what was determined to be the actual cause of the asthma and do not take into account positive skin reactions to substances to which the patient was not exposed—that is, if a patient gave positive skin reactions to ragweed and dog epithelium, but did not come in contact with dogs and only had asthma in the autumn with hayfever, he is listed as a pollen asthma and not as a mixed asthma. Thus the figures for “mixed” asthmas do not represent the actual number of cases of multiple hypersensitiveness, which would be considerably higher than those given in the table.

Year.	Number of cases.	Pollen, per cent.	Undiagnosed, per cent.	Mixed, per cent.	Animal, per cent.	Bacterial (questionable), per cent.	Food, per cent.	Dust.
1917 . . .	135	38.5	29	14	9	8	1.5	0
1920 . . . (6 mos.)	122	24.0	17	38	5	10	2.0	4

A study of this table reveals several interesting points: (1) Our undiagnosed cases are decreasing as our knowledge increases; (2) the mixed cases increase at the expense of the pure pollen and animal cases; (3) the food and bacterial cases remain about the same and are a small percentage of the whole; (4) we have discovered a new and very important class of exciting agents, the dusts, which, while they affect a very small number of people as a pure group, account for most of the increase in the mixed class.

The preceding table gives the percentage of the different classes of asthma, but it is of interest to know something of the relative frequency of sensitiveness to the most common substances. A study was made of 100 consecutive cases of hypersensitiveness, excluding uncomplicated hay fever, and the results are given in the following table. All cases were not tested with every substance, but where less than twenty tests were made with any single extract it was excluded from consideration in the table:

EXTRACT	RAGWEED	DUST	ORRIS	CHICKEN EPITHELIUM	HAY	COW EPITHELIUM	HORSE EPITHELIUM	CAT EPITHELIUM	TIMOTHY	STRAW	RABBIT EPITHELIUM	DOG EPITHELIUM	DOG SALIVA	PUCK EPITHELIUM	GOOSE EPITHELIUM	HORSE SERUM	COTTON	LE PAGE	SHEEP EPITHELIUM	KAPOC
NUMBER OF CASES TESTED	99	91	94	92	47	71	94	91	90	25	93	92	83	74	91	68	61	78	57	53
PERCENTAGE REACTING																				
30																				
25																				
20																				
15																				
10																				
5																				

A study of the chart shows that ragweed and dust most frequently gave positive reactions; the former being twice as common as timothy. Chicken epithelium and orris were also common. Hypersensitiveness to horse epithelium was nearly five times as frequent as to horse serum.

Similar tables have been made for the various foods, but it is felt they are of little value because of the unreliability of the food skin reactions as referred to above.

Having made our diagnosis by the aid of the history and cutaneous reaction, what can we do in the way of treatment? First, we must learn to discard the word "cure." Once an asthmatic a patient is usually a potential asthmatic for the rest of his life, just as a diabetic is potentially a diabetic whether his urine is sugar-free or not. Many do outgrow their hypersensitiveness as we all know, but it pays to take no unnecessary chances in waiting for this occasional happy result to occur. The one rule to follow is, "Remove from the environment of the patient all causative factors that can be removed and immunize him against all those that cannot be otherwise controlled." For example, we find a patient hypersensitive to ragweed, cat epithelium, chicken epithelium and several foods. We advise him to allow no cats in his house, substitute silk floss or cotton pillows for his feather ones, have several thorough house-cleanings to remove all the feather dust already present in his house dust; omit the particular foods from his diet, and then immunize him with ragweed pollen injections during the season. If we omit any one of these procedures (except possibly the diet) he will probably continue to have his asthma as before; and if, in spite of all these procedures, he continues to

have asthma it means we have overlooked some other cause. In at least 80 per cent of all cases we can get skin reactions to one or more extracts, and in a large percentage of these a satisfactory result can be obtained if the patient is willing to follow directions. This latter point is important, and much depends on the intelligence of the patient. When in spite of demonstrable evidence in the way of skin reactions he refuses to believe that a feather pillow, which he has treasured for years, may be the cause of his trouble, or insists that the presence of the cat in the house can have nothing to do with his discomfort, as he never picks it up, it is hopeless to try to benefit him. But if he once grasps the idea (and with marked skin reactions it is usually easy to persuade a person that that particular substance is not a good one to allow in contact with his bronchial mucous membrane), the battle is more than half won, and one has secured a valuable ally in his fight.

If the result is not at first successful it does not mean that the patient faces asthma for the rest of his life, and this should be explained to him. We are constantly finding new causes, and a case which resists treatment now may yield very readily and simply six months from now, when our knowledge is greater. During the past year we have made a great advance in solving many of our so-called "dust cases." In 1917, we found that many of our cases gave marked skin reactions to extracts of dust collected from their houses (preferably with a vacuum cleaner). These reactions are not necessarily individual—that is, if a patient reacts to one dust he may (and usually does) react to several or all, although occasionally we find a case reacting to his own dust and no other. It is difficult to find out the exact ingredients of dust, but it is probably chiefly made up of feather dust, orris and insecticide powders, stuffing of mattresses and upholstered furniture, animal emanations from household pets and from rabbit hair, commonly used as filling for sofa pillows and cushions. Extracts can be made from each separate pillow, mattress, couch stuffing, etc., and the patient tested with these often gives positive reactions from one or two and negative from the rest. The articles giving positive reactions are then removed from the house, and after a thorough house-cleaning the whole dust is again tested; if it is negative we can be sure that the cause of the trouble, in that direction at least, has been removed.

The whole procedure, unfortunately, is not as simple and satisfactory as these few words would seem to indicate. All too often the feather pillows are removed from the bedroom, a thorough house-cleaning is done and the patient is well and happy for five or six weeks, only to come back at the end of that time with a return of the asthma. In many of these cases the explanation lies in the gradual filtering in of the dust from other rooms where feather pillows still abide and a gradual loss in zeal of the house-

cleaner. It is easier to accomplish results in the homes of the well-to-do, where the rooms can be better isolated and where the patient and his family are intelligent in their coöperation. Unfortunately many of our clinic cases come from the tenements, where six or eight people live in four or five closely connected rooms, speak our language imperfectly and have not the vaguest idea what all the commotion is about. They want a good asthma medicine to take internally. In the clinic which we have been conducting at the New York Hospital for the last year this difficulty showed itself at the start and our results were discouraging. We solved part of the problem by the aid of a visiting nurse who went to the homes, collected samples of dust, saw that our recommendations were being carried out and had a chance to explain more fully our object. Results improved but still left much to be desired, and now we are trying to supplement our work by making up extracts from the dusts from the various homes, and, if they give good skin reactions, using them for active immunization as we do pollen extracts. This is, of course, in conjunction with the removal of any definite exciting cause and thorough house-cleaning. Since then we have been able to see a marked improvement in our results, but it is still too early to say how much we can accomplish. This much can be vouched for, that the idea is gradually spreading among our patients that dust in a home is not lucky for an asthmatic and that silk floss or cotton pillows are often better than those made of feathers or rabbit hair. One patient who improves teaches the others, and in time I hope the new conception of asthma will be as well known among the laity as the cause and prevention of tuberculosis now is.

So far nothing has been said about bacterial extracts and bacterial vaccines over which so much enthusiasm has been raised in the last few years. Sicard<sup>5</sup> published in 1917 a series of cases of bronchial asthma treated by vaccination with apparently satisfactory results. In 1919 Walker<sup>6</sup> reported on the treatment of asthma by bacterial vaccines and bacterial extracts. He divided his groups into those that gave positive cutaneous reactions to bacterial proteins (7 per cent in a series of 400), and those treated with bacterial extracts or vaccines that had shown no positive cutaneous reaction to any substance with which they were tested. In the first group, those that were sensitive to bacterial proteins, treatment was carried out by the injection of vaccines of the same bacteria, and the author records 75 per cent of the patients of this group as having been relieved of their asthma. Of the non-sensitive patients treated with bacterial vaccines only 37.5 per cent were relieved of asthma and 25 per cent were markedly improved.

<sup>5</sup> Treatment of Bronchial Asthma by Vaccination, with report of Cases, *AM. JOUR. MED. SC.*, 1917, 158, 856.

<sup>6</sup> Treatment of Bronchial Asthma with Vaccines, *Arch. Int. Med.*, 1919, 23, 220.



Later, Raekeman<sup>7</sup> published the results of his observations on 39 patients, and concludes that the treatment was successful in fairly close accordance with the presence of a positive skin test.

Our own experience with bacterial extracts and bacterial vaccines has been so unsatisfactory and so out of accord with the figures given above that it seems necessary to subject the whole question to a more careful and critical review.

Karl F. Meyer<sup>8</sup> has shown that cutaneous hypersensitiveness to bacterial proteins is only induced by an active infection. Further, he has shown that this hypersensitiveness is only temporary. If the treatment of asthma is specific it should be possible to demonstrate the presence of that particular organism, in the sputum or elsewhere, to the protein of which the case shows a cutaneous reaction. This, however, has not been possible, as stated by Walker and amply substantiated in our own cases.

In addition, if a bacterial protein giving a positive cutaneous reaction is in fact the real cause of the asthmatic manifestation in any individual, then the injection of such protein subcutaneously in sufficient amounts should produce a constitutional reaction manifested by an acute attack, as can be done so readily with the epithelial and pollen extracts. In spite of many attempts no such result has yet been obtained.

Another test of the hypothesis that bacterial proteins are themselves causes of asthma would be the therapeutic efficiency of bacterial vaccines or extracts. In our own cases treated in this way, satisfactory results are not obtained in more than 10 per cent of the cases, and this is such a small percentage that the apparent improvement can readily be attributed to unknown factors.

It is a great mistake to consider bacterial infections as true etiologic factors for hypersensitiveness in the sense in which that term is used today. Cases of asthma that cannot be diagnosed by cutaneous tests with pollens, animal emanations, sachet powders, drugs or foods have conveniently been considered as examples of the bacterial reactions. A study of our records of five years ago shows that we were diagnosing but 50 per cent of the cases, whereas today we are able to diagnose 73 per cent, not counting the so-called bacterial group. This improvement has all been at the expense of the so-called bacterial cases.

All of which shows that the more carefully this subject is studied the greater is the percentage of those that can be definitely diagnosed without any regard for the hypothetical bacterial hypersensitiveness. I do not wish to be understood as saying that bronchial infection does not occur, for of course it does; and we must remember that secondary infections occur wherever con-

<sup>7</sup> The Relation of Sputum Bacteria to Asthma, *Jour. Immun.*, July, 1920, No. 4, 5.

<sup>8</sup> A Résumé of Some Experimental Studies on Cutaneous Hyper-sensitiveness, *Am. Jour. Dis. of Children*, December, 1919, 18, 577-590.

gested and edematous mucous membrane exists. In some cases of secondary bronchial infection of long standing, autogenous vaccines given in gradually increasing doses over a period of time may bring about definite improvement as far as the infection itself is concerned, but it will not affect the asthmatic manifestation. Needless to say, manifest pathologic conditions of the nose and throat, such as polypi, deviation of the septum, hypertrophy of the turbinate bones or infected tonsils, must be appropriately treated surgically. But it must also be borne in mind that polypi may be the sign of a chronically edematous, hypersensitive mucous membrane rather than an infected sinus, and that removal of the specific factor will go a long way toward clearing up the associated infection.

I have spoken at length as to treatment by removal of the cause. Now for a few words as to treatment where the cause cannot be removed. This is usually the case with pollen asthmas, for while some of them can get away during the season, many cannot, and in any event it is a real hardship to be obliged to leave one's home when it may be not convenient. Pollen asthma is treated precisely as the associated hay fever by pollen extract injections with about 80 per cent satisfactorily relieved, a better record than that of the associated hay fever. The injections not only relieve the asthma but minimize the danger of subsequent bacterial infection and the production of a chronic bronchitis or sinusitis. They also lessen the danger of a rhinitis and bronchitis during the succeeding winter. It is occasionally necessary to immunize against horse, dog or cat epithelium, and this too can be done very successfully, but it must be remembered that the immunity is not permanent, and it is necessary to give injections once a month or so to maintain it. I have already spoken of giving injections of autogenous dust, and this has been a great help in controlling our dust asthmas, particularly in our clinic cases.

In children hypersensitive to milk, eggs or wheat it is often a difficult problem to decide what to do. If they are hypersensitive to but one of the three it is better not to try immunization but to omit that article of food from their diet until they naturally outgrow their hypersensitiveness. Where all three are involved it is difficult to make up a nourishing diet without them. Often they can take goat's milk instead of cow's milk. It is possible to immunize them against any one of the three by injections of the protein or by feeding minute quantities by mouth, but it is a difficult, tedious process and often unsuccessful. Park<sup>9</sup> reports a case of immunization to cow's milk where an initial dose of one drop, well diluted, gave a marked constitutional reaction.

Results of treatment of asthma are more difficult definitely to

<sup>9</sup> A Case of Hypersensitiveness to Cow's Milk, *Am. Jour. Dis. of Children*, January, 1920, 19, 46-54.

determine than those of hay fever. The latter is limited to a certain time of the year, and at the end of the season it is possible to get a fairly accurate estimate of the condition during exposure. With most of the asthma cases, except those due to pollen, it is an all-year-long affair, and it is difficult to follow the patients indefinitely. They may not report because they are entirely well and do not think it necessary; or because they are fairly well and too busy to bother about it; or because they are just as bad as ever and disheartened at their failure to find relief. A careful study of the 122 cases cited under the first six months of 1920 has shown that from the histories and questionnaires sent out we have data enough on 67 patients (excluding the 17 per cent undiagnosed) to make a fairly accurate estimate of their results six months to a year after treatment. Using the same classification as with hay-fever we find 40 per cent in Class A, 35 per cent in Class B, 15 per cent in Class C and 10 per cent in Class D. This is not put forward as an accurate statement of the end-result of the treatment of all asthma cases, as the number is entirely too small, but is merely an indication that probably 75 per cent of all asthma cases, where a diagnosis can be made, can be brought to a state of comparative comfort. Those cases due to animal epithelia do best, with the pollen, food, mixed and bacterial asthmas following in the order named.

**Conclusion:** In conclusion, I wish to cite the history of a typical "dust case," illustrating the difficulties encountered in such cases and the eventual success obtained with careful management and treatment.

The patient was a woman, single, clerk, aged twenty-eight years. She had had asthma since five years of age, almost continuously for the past few years, and with acute exacerbations which kept her from working. She had had several nose and throat operations without relief. Skin tests were positive for ragweed, chicken feathers and orris. The attack which brought her under our observation, lasting six weeks, coincided with the gift from a friend of a box of highly scented talcum powder. She lived in a single room in a girls' dormitory with eight other girls on the same floor. She moved into a new room which had been carefully cleaned and was without feather pillows or talcum powder. Her asthma promptly cleared up and she stayed well for three months, going to work every day. She then began to have a little asthma and further tests were made which showed, among other things, a hypersensitiveness to rice powder. This was an ingredient of a new face powder she had just begun to use and its removal promptly cleared up the asthma. She was then well for six weeks until she went home for a visit. Her case had been explained to her family, but they did not believe in such nonsense, and no effort was made to clear her room of feathers until she arrived, when she

removed the pillows herself. After one night there she developed asthma, which cleared up on her return to New York. In September she took a trip to Pennsylvania during the height of the ragweed season, and although she had been receiving ragweed injections and was perfectly comfortable in New York, the doses evidently had not been sufficient and she developed asthma during a dusty automobile ride. This cleared up on returning to New York and she remained well for two months, when severe asthma returned and no cause could be found to account for it. It then occurred to us that her room might have become saturated again with dust from the rooms of the other girls on the same corridor, as it was swept out into the hall and past her door without any special effort being made to keep it out. An extract was made from dust collected from a small rug near her bed which had not been beaten for a long time, and this gave a marked positive skin reaction. Her room was again carefully cleaned, the rug beaten every few days, the door closed while the corridor was being swept and she was given injections of her own dust extract. Her asthma gradually cleared up and she has been practically free for eight months, with the exception of a few slight attacks which have not prevented her from working.

To some this may not seem like a particularly brilliant result, as she has had three or four attacks of asthma during the past year; but they have all been short ones and she has been able to work practically all the time instead of being confined to bed for a week or two every month. She is intelligent and anxious to help herself, and knowing her various hypersusceptibilities she will be more able to avoid the causes of them in the future. The less asthma she has the less she is likely to have, and she may in time entirely outgrow her hypersensitiveness.

### SYPHILITIC BACKACHE.

BY WARREN THOMPSON, M.D.,

OMAHA, NEB.

BACKACHE presents one of the common and frequently one of the most difficult problems arising in the course of a day's work. Among the many causes for this complaint, syphilis has received but little attention. Two cases which presented themselves with a chief complaint of backache, in whom syphilis of the spine was diagnosed, seemed sufficiently interesting and instructive to warrant a report and a brief review of this condition:

CASE I.—Mrs. V. A., aged fifty-nine years, 1916, housewife. Two children living and in good health. There have been no miscarriages.

*Past Illness.* She stated that she had always enjoyed good health until the onset of the present trouble.

*Present Illness.* The patient was admitted with a chief complaint of backache, affecting the lower dorsal and lumbar regions. The trouble began five years ago with a dull ache, which came on after a hard day's work. Rest always relieved it at that time. Last winter the "bad back" began to trouble again and the pain was described as "pulling like." The attacks were repeated every few weeks, but were always relieved by rest. Four months ago the back trouble became more constant and lying down gave no relief. The pain was dull and was described as "though the muscles were all drawn up in the lower part of the back." The backache was particularly troublesome at night. Pressure over the aching parts increased the pain. The patient had been confined to bed for the past seven weeks on account of the pain. The pain bore no relation to urination, defecation or menstruation—in fact the menopause had come on eight years previously. Weather changes did not influence the backache.

*Physical Examination.* The patient was a poorly nourished, sallow woman. The teeth had all been extracted. The tonsils were buried. The cornea of the right eye was hazy and the patient stated that it had been so since a girl of thirteen. The pupils were irregular and reacted sluggishly to light. There was a slight systolic whiff at the apex and a somewhat accentuated second sound at the base. Nothing noteworthy was found in the examination of the lungs or abdomen. The back was rigid from the tenth dorsal vertebra on down. Percussion over the lower dorsal and lumbar vertebræ caused pain. No tumor masses could be palpated along the spine. There was a slight curvature to the left. Attempted motion was restricted in all directions and produced pain.

The pelvic examination was negative.

The urine, stomach contents and stool examinations were negative. The blood Wassermann was three plus positive. On account of the fixation of the spine a spinal tap was not attempted. Radiograms showed a thickening of the periosteum with some bony deposits at the tenth, eleventh and twelfth dorsal vertebræ.

Vigorous antiluetic treatment was instituted and the backache gradually subsided after four weeks in the hospital.

Although the patient neglected to return for further observation, serologic tests and treatment, in answer to a recent communication she reports that she has been entirely free from backache since her departure from the hospital.

CASE II.—Mr. I. A., aged thirty-eight years, farmer, consulted me for backache October 21, 1916. One child living and in good health.

*Past Illness.* Negative. The patient denied venereal infection.

*Present Complaint.* The chief complaint was backache, affecting the left side of the spine at the level of the tenth dorsal to the first lumbar vertebra. He has not noticed any local tenderness. Bending or stooping did not increase the pain. He stated that it was somewhat worse after lying down. The weather at times seemed to affect the pain, it being worse in damp, cold weather and easier during warm weather. Last year the patient had what he called "sciatica" in the left leg. His backache was always worse at night.

*Physical Examination.* A poorly nourished, sallow man, who appeared older than his stated age. The teeth were in good condition and the roentgen-ray films were negative. The tonsils appeared normal, there being no injection of the pillars and no palpable cervical glands. The pupils reacted slowly to light and normally to accommodation. The left pupil was irregular. The right abdominal reflex was not so marked as the left, the lower right being nearly absent. The knee-jerks, ankle-jerks and other reflexes were normal. There were no sensory changes.

There was some fixation of the lower dorsal and lumbar vertebrae. Percussion over this area produced excruciating pain, especially on the left side at the level of the first lumbar vertebra. Motion was somewhat limited but did not increase the pain materially. No tumor masses were palpable.

The right tibia was very rough and tender to palpation and to percussion.

Nothing noteworthy was found in the examination of the heart, lungs and abdomen.

The urine examination was negative.

The blood Wassermann was four plus positive. The spinal fluid showed increase in globulin, cell count 16 and Wassermann four plus.

Radiograms of the spine were negative.

The patient was put under antileptic treatment and the relief from the backache was complete. Likewise the spinal fluid and blood Wassermann were negative.

There was no return of the backache until February, 1921. Physical findings at the time were practically the same as at the time of the original examination. The spinal fluid showed a cell count of 4. The globulin, colloidal-gold and Wassermann tests were negative. The blood Wassermann was four plus positive. A roentgen-ray plate of the spine was negative. The backache has again entirely disappeared after antileptic treatment.

*Remarks.* The occurrence of syphilis elsewhere in bone tissue has been frequently recognized and is not particularly uncommon. Syphilis of the vertebral column, however, although rather a rare condition, is probably frequently overlooked. Whitney<sup>1</sup> in the

<sup>1</sup> Syphilis of the Spine: Its Frequency and the Value of its Characteristic Lesions as a Diagnostic Sign in Syphilis, Jour. Am. Med. Assn., 1916, 66, 627.

examination of 544 syphilitics studied at the University of California Hospital, diagnosed syphilitic joint disease in 83, or 15.2 per cent, and of this number 41 showed involvement of the spine. Although syphilis may affect any part of the spine the most frequent sites are the cervical and lumbar regions, over one-half the reported cases affecting the cervical vertebrae. Hunt<sup>2</sup> gives the following figures in 88 cases collected by Ziesche: Cervical cases, 61; dorsal cases, 12; lumbar cases, 5; sacral cases, 2; cervical and dorsal, 1; dorsolumbar, 3; diffuse, 4. Age does not seem to be a factor, as it has occurred in cases of hereditary lues as early as four years and as late as sixty in acquired cases. It usually is a tertiary manifestation; however, it has been suggested that the backache so common during the secondaries may possibly be due to a mild periostitis occurring at that time. Trauma is a probable factor and may explain the high percentage of cervical cases. In cervical cases the frequent association of pharyngeal ulcers and gummata has been noted and the possibility of direct extension to the spine has been suggested (Hunt).<sup>3</sup>

**Symptoms.**—Pain is usually the chief symptom. It may come on suddenly, similar to that produced by an acute focal infection, or the onset may be gradual, extending over a prolonged period of time, manifesting itself by a general soreness. It is generally definitely localized in the part of the spine involved unless there is an associated involvement of the posterior nerve roots or the cord itself, in which cases the distribution or radiation of the pain varies accordingly. One very characteristic and diagnostic feature lies in the fact that the pain, although quite constant, is invariably greatly intensified at night. (This information was volunteered by both cases herein reported.) Local tenderness is marked, which becomes acute on percussion over the affected area. There is limitation of motion and attempted movements of the spine show increased rigidity and aggravate the pain. Whitney states: "The characteristic thing is not the hypertonicity alone, but this combined with a stiff back or with a back showing areas of restricted mobility. This combination of two findings we have regarded as almost sure proof of syphilis, and it is one of the points we especially desire to emphasize in this paper, that in this we have a pathognomonic sign which is of quite as much interest to the general diagnostician as to the orthopedist." If the bony involvement is extensive slight swelling or considerable tumefaction is visible. Attention has been called particularly by Sachs,<sup>4</sup> Hunt<sup>5</sup> and Wholey<sup>6</sup> to the bizarre

<sup>1</sup> Syphilis of the Vertebral Column: Its Symptomatology and Neural Complications, *AM. JOUR. MED. SCI.*, 1914, 147, 164.

<sup>2</sup> *Loc. cit.*

<sup>3</sup> Specific Vertebral Osteitis Simulating Specific Pachymeningitis. Section on Neurology and Psychiatry, New York Academy of Medicine, January, 1913.

<sup>5</sup> *Loc. cit.*

<sup>6</sup> Complicated Nerve Tissue Involvement Arising from Syphilis of the Vertebrae, *Jour. Am. Med. Assn.*, 1916, 66, 627.

nervous symptomatology which may arise, presenting no characteristic picture but depending on the location and extent of the nervous involvement. Wholey<sup>7</sup> remarks: "Frequently it is through some manifestation in the widely varying symptomatology arising from nervous involvement that the existence of osseous disease is suggested rather than through any symptoms arising directly from the spondylitis."

**Pathology.**—The pathology is similar to bone syphilis elsewhere. It may be a simple periostitis, an osteitis or a combination of both, depending on the extent of the process. Syphilis tends to form new bone, and the nodules which thus arise frequently make pressure on nerve roots, thereby acting mechanically as a factor in the production of pain. Gummatous formation in the body of the bone may undergo liquefaction necrosis. Charcot's joints may involve the spine, and although still a moot question as to whether such joints are truly syphilitic or parasyphilitic, similar symptomatology may arise. Kerr<sup>8</sup> states that only 2 cases of Charcot's joint involving the spine were recorded out of 300,000 cases seen in the outpatient department of the Massachusetts General Hospital in three years. Whitney<sup>9</sup> calls particular attention to a synovitis, the synovia of the various spinal joints being attacked, "Leading at first to lessened motion from spasm, but as the acuteness of the process subsides, adhesions are usually formed which limit motion and in many cases give complete fixation." Roberts<sup>10</sup> states that "There is sufficient evidence that backache may in some instances be due to a myositis caused by syphilis toxins to warrant further investigation of this subject." The nervous pathology is a result of the compression of the spinal cord and nerve roots incident to the spondylitis. If the disease is extensive a compression myelitis may develop at the level of the bony involvement. Spontaneous fracture may be an end-result, particularly in the Charcot joints (Kerr).<sup>11</sup>

**Diagnosis.** The diagnosis of syphilitic backache necessitates the careful exclusion of all other possible factors producing backache. The various causes in the production of backache are too numerous to justify any attempt at a detailed differential diagnosis in this paper. Special attention, however, should be called to several conditions with which it is particularly liable to be confused, namely, osteoarthritis from focal infection, tuberculosis, metastatic invasion of the spine from malignant tumors and typhoid spine.

Infective arthritis usually involves many vertebræ, whereas syphilitic spondylitis is characterized by the limited number of

<sup>7</sup> Loc. cit.

<sup>8</sup> Report of Three Cases of Syphilis of the Spine and Three Cases of Spontaneous Fracture, *Jour. Nerv. and Ment. Dis.*, 1916, 44, 346.

<sup>9</sup> Loc. cit.

<sup>10</sup> Syphilis as a Cause of Backache, *New York State Jour. Med.*, 1919, 19, 20-24.

<sup>11</sup> Loc. cit.



vertebræ involved. In Ziesche's series, quoted by Hunt,<sup>12</sup> the following figures are significant as to the number of vertebræ involved: 1 vertebra in 25 cases, 2 vertebræ in 17 cases, 3 vertebræ in 11 cases, 4 vertebræ in 3 cases, diffuse in 4 cases.

Tuberculosis is particularly liable to be confused. Sloan<sup>13</sup> states that in a series of 70 cases of supposedly tuberculous spondylitis cases in the Foundling Hospital in London, 7 per cent showed positive Wassermann reactions and cleared up under antiluetic treatment. Roberts,<sup>14</sup> in his remarks on syphilis as a cause of backache, states that probably 50 per cent or more of the conditions which we have heretofore ascribed to tuberculosis are really of luetic origin. Roentgen-ray findings and evidence of tuberculosis elsewhere in the body are helpful in differentiating these conditions.

Typhoid spine must be considered but is usually readily differentiated by roentgen-ray evidence and the history of a previous typhoid infection.

Metastatic invasion of the spine demands a careful search for a primary malignancy, and this, combined with rather definite roentgenologic findings, makes for a positive diagnosis.

The roentgen-ray is a valuable aid, and yet in early lesions the findings are often negative. Periostitis is manifested by a diffuse thickening of the periosteum with possibly some bony deposits. New-bone formation is a characteristic of syphilis involving the bone. Gummata involving the body of the spine with little evidence of new-bone formation are particularly confusing, the differentiation of this condition from tuberculosis or metastasis from malignant tumors being difficult. In more advanced cases of syphilitic spondylitis the picture is so definite that the roentgenologist can make the diagnosis unaided.

*The Wassermann Test.* The Wassermann, when positive, is a valuable adjunct in diagnosing syphilis affecting any part of the body. It must be remembered, however, that the Wassermann test is frequently negative in syphilis of bone. An exact explanation of this fact is wanting, but Sloan<sup>15</sup> suggests that the rather poor blood supply to bones might account for the smaller percentage of positive reactions in bone syphilis than in syphilis involving the soft tissues. Examination of the spinal fluid should be made whenever the fluid is obtainable, as it is now an established fact that a blood Wassermann in certain cases is often negative when the spinal fluid Wassermann is sharply positive.

A careful search for evidenc of syphilis elsewhere in the body is of the utmost importance. Irregular pupils or other manifestations of central nervous system involvement are helpful in arriving at a final diagnosis.

<sup>12</sup> Loc. cit.

<sup>13</sup> Syphilis of the Spine, Cleveland Med. Jour., 1914, 12, 30-5.

<sup>14</sup> Loc. cit.

<sup>15</sup> Loc. cit.

**Therapeutic Test.**—The remarkable response of bony syphilis to antiluetic treatment holds true in syphilis of the spine. The bony deposits if present readily disappear and the pain, if due to the spondylitis alone, rapidly subsides.

**Prognosis.**—Insofar as the backache resulting from syphilitic spondylitis is concerned the prognosis is excellent, particularly in early cases properly treated. The chief concern rests in the nerve and cord involvement, the outcome of which is always uncertain.

**Treatment.**—The principles in treatment of syphilis apply here as elsewhere. Cases should be controlled with subsequent Wassermanns and roentgen-ray plates. Patients with extensive destruction of the spinal column demand the coöperation of the orthopedist.

**Summary.**—1. Backache as a chief complaint may be due to syphilitic spondylitis, and although the condition is rare it should be considered as a possibility in every indefinite case of backache.

2. Syphilis may involve any part of the spine; the most frequent location, according to the literature, is in the cervical vertebræ.

3. The pathology is similar to syphilis of bone elsewhere in the body. The nervous manifestations depend on the part of the vertebral column involved and the extent of the morbid process.

4. Syphilitic spondylitis presents no definite clinical picture, the diagnosis being made chiefly by (1) the roentgen-ray, (2) evidence of syphilis elsewhere in the body, (3) the Wassermann test, and (4) the therapeutic test.

---

## THE INCIDENCE OF CECAL TUBERCULOSIS WITH PULMONARY TUBERCULOSIS.\*

BY I. H. LEVY, M.D.

PROFESSOR OF MEDICINE, SYRACUSE UNIVERSITY.

AND

H. H. HAFT, M.D.

SYRACUSE, N. Y.

THE subject of tuberculosis is particularly interesting to the gastroenterologist, as digestive symptoms are so frequently the first manifestation of early lung involvement. Then throughout the entire course of the disease a good gastro-intestinal tract is almost a *sine qua non* for recovery. To build up the body resistance an abundance of good, nourishing food must be digested and assimilated. If a tuberculosis patient who has been progressing favorably so far as his pulmonary condition is concerned, reaches a period of standstill or begins to lose ground, there is likely, especially if associated

\* Read at the Annual Meeting of the American Gastro-enterological Society, at Boston, Mass., June 6, 1921.

with gastro-intestinal symptoms, to be an involvement of the alimentary tract. These symptoms are anorexia, slight bloating, belching, intestinal discomfort or pain usually localized in the mid or lower abdomen. The pains are crampy in character, suggesting gas pains, and come on at irregular intervals, and are likely to be aggravated by eating. There may be fever not due to the lung condition; also, alternating diarrhea and constipation.

Tuberculous colitis is by no means an infrequent complication of pulmonary tuberculosis. Pathologists tell us that from 70 to 90 per cent of all tuberculous patients show involvement of the gastro-intestinal tract, and Albrecht<sup>1</sup> states that with cavity formation practically all do. It is interesting to note that even Hippocrates<sup>2</sup> recognized the seriousness of diarrhea in consumption, for he says in his aphorisms that diarrhea attacking a person with phthisis is a mortal symptom. The site of the ulcerative lesion, as found by Fenwick and Dodwell<sup>3</sup> in 500 autopsies was as follows: Ileocecal region, 85 per cent (confined to this region alone, 10 per cent); jejunum, 28 per cent; duodenum, 3.4 per cent; ascending colon, 51.4 per cent; descending colon, 21 per cent. The cecum is probably the part first involved and the process extends in both directions. As to the method of infection, it may be either direct from swallowed sputum or the bacilli may be carried by the mesenteric vessels.

Ileocecal tuberculosis in its early stages, at least, is difficult to diagnose by the ordinary clinical methods: Neither the symptomatology, physical examination nor the ordinary laboratory findings give the necessary information. The history points to gastro-intestinal tract involvement, but does not differ materially from that of other conditions, like chronic appendicitis and the non-tuberculous forms of colitis. Alternating constipation and diarrhea, while suggestive, are not always present. Physical examination elicits sensitiveness in the cecal region, and frequently, especially late in the disease, a thickening or tumor can be palpated. Likewise the laboratory findings are of little value. The presence of tubercle bacilli in the feces does not establish the diagnosis, as it has been shown that they exist in the gastric and intestinal contents of patients with pulmonary tuberculosis without any intestinal involvement. Given, then, a patient with pulmonary tuberculosis exhibiting gastro-intestinal symptoms associated with some pain and thickening in the ileocecal region the evidence is favorable to the diagnosis of intestinal tuberculosis. If alternating diarrhea and constipation are also present the diagnosis is almost certain. But to wait until the fully developed symptom-

<sup>1</sup> Frankf. Z. f. P., 1907, 1.

<sup>2</sup> The Genuine Works of Hippocrates, translated by Francis Adams, William Wood & Co., Aphorisms 14, Section V, p. 236.

<sup>3</sup> Lancet, July 16, 1892.

complex is present before making a diagnosis is like refusing to diagnose cancer of the stomach until lactic acid and Boas-Oppler bacilli are found in the gastric contents and a palpable tumor is present. The early diagnosis of the former is just as important as the latter.

Stierlin,<sup>4</sup> of Basle, was the first to call attention to the roentgen diagnosis of ileocecal tuberculosis. In 1911, he reported 6 cases—4 of tuberculous colitis, 1 of cancer and 1 of ulcerative colitis—in which he was unable to fill the cecum and descending colon with the opaque meal. All of the cases were operated upon and the roentgen findings verified. He says in the main: "In infiltrating and ulcerative involvement of the cecum and ascending colon there is an absence of the normal shadow of this part of the colon, as shown in the skiagram six or seven hours after the barium meal, while the terminal ileum and transverse colon are filled. Consequently the early as well as the later stages of the so-called cecal tuberculosis can be diagnosed by this means, even in cases undiagnosable by the ordinary clinical methods."

In 1912, Case,<sup>5</sup> in a paper discussing tuberculosis of the ileocecal region, says: "Ileocecal tuberculosis is a condition which in a certain number of cases can be almost surely diagnosed by the roentgen-ray examination."

In 1917, Pirie,<sup>6</sup> of Montreal, at the request of Dr. Archibald,<sup>7</sup> made some roentgen-ray studies of intestinal tuberculosis. His report is worth quoting:

"Dr. Archibald has asked me if I could write from memory a summary of my findings in tuberculosis conditions of the intestines. I do so with pleasure, as it was about the most interesting work I did for about a year before the war began. Writing as I do without notes from a base hospital in France, I well remember the disappointment we had, as in several successive cases of tuberculous cecum I failed absolutely to help in the diagnosis. Some bad luck seemed to dog my steps, for whereas we had formerly been able to show by means of a barium meal the position, shape and size of the normal cecum, yet we failed, in these tuberculous cases, to catch the cecum at the proper time when it was filled by the meal. Finally the cause of our failure struck us. We could not show the cecum filled by a barium meal because it never did fill when tuberculous ulceration existed. Setting out with this as a working hypothesis we examined the cases at half-hour intervals from four to twelve hours after the barium meal. We found our theory correct in each case of tuberculous cecum, namely, the

<sup>4</sup> München. med. Wehnsehr., 1911, 58, 1231.

<sup>5</sup> X-ray Studies of the Ileocecal Region and the Appendix, Am. Quart. Roentgenol., 1912.

<sup>6</sup> See Archibald's Article.

<sup>7</sup> The Role of Surgery in the Treatment of Intestinal Tuberculosis, Am. Rev. Tuberc., October, 1917, p. 449.

cecum never filled up with the meal. Each small squirt of barium that left the ileum was quickly passed on past the cecum and collected elsewhere in the large colon, either in the transverse or the descending part. So that our conclusion was that in a tuberculous subject with symptoms suggesting tuberculous cecum, if the cecum did not fill from four to twelve hours after the barium meal when examined at intervals of about half an hour, then this want of filling confirmed the diagnosis. On the other hand when it did fill, as it does in a normal individual, it negated the diagnosis of tuberculous cecum. We had this latter experience confirmed in one case where a clinical diagnosis of tuberculous cecum



FIG 1 —Barium enema. Normal colon. Complete filling of cecum at "A"

had been suggested: The roentgen ray showed a cecum filled by barium, and at operation a non-tuberculous cecum was found."

It was not, however, until 1919, when Lawrason Brown<sup>8</sup> and Homer Sampson, of the Trudeau Sanitarium, published their work on the *Early Diagnosis of Ulcerative Tuberculous Colitis*, that this subject received the attention it deserved. They observed a large number of cases and confirmed *in toto* the work of Stierlin and Pirie. Of their 175 cases of pulmonary tuberculosis examined, 44 were positive, and of these, 28 were operated upon and 27 found

<sup>8</sup> Early Roentgen Diagnosis of Ulcerative Tuberculous Colitis, *Am Jour Roentgenol*, 1919, 6, 625 Early Roentgen Diagnosis of Ulcerative Tuberculous Colitis, *Jour. Am. Med Assn*, July 12, 1919, p. 77.

to be correctly diagnosed. Since then Carmen,<sup>9</sup> from the Mayo Clinic, and others have added to the literature of this subject. The severity of the lung involvement does not necessarily correspond with that of the intestine. The former may be very slight, even arrested, while the latter may be extensive and active.

Pässler,<sup>10</sup> in 1911, reported 2 cases of extensive colon involvement running an acute course and terminating in death with very little lung involvement.



FIG. 2.—Incomplete filling of cecum at "A."

Our paper is based on a study of 80 cases of tuberculosis, examined roentgenologically: 70 of these are patients at the Onondaga County Tuberculosis Sanitarium, the majority having fairly well-advanced lesions. We have also in our routine work examined about 4000 patients and have especially during the past year observed the colon very carefully.

**Technic.** With few exceptions the barium enema (Holzknecht's formula) was employed. If the entire colon filled we assumed

<sup>9</sup> Roentgenology of Tuberculous Enterocolitis, Jour. Am. Med. Assn., May 15, 1920, p. 1371.

<sup>10</sup> München. med. Wehnschr., October 23, 1906, p. 2090,

that the case was negative, although we knew that slight lesions might be present despite a completely filled colon. Those cases which failed to fill we had to return for an opaque meal, which consisted of four ounces of barium suspended in a pint of malted milk thickened with cornstarch. Six hours later the patient presented himself for observation, having abstained from food in the interval. Observations were made at half-hour intervals until

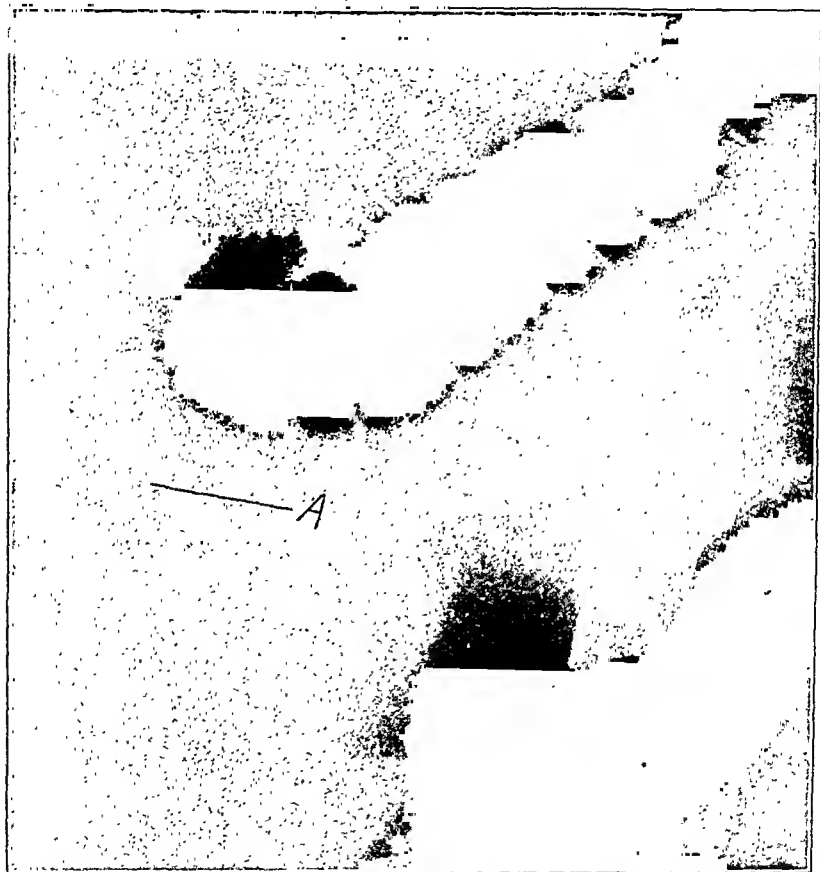


FIG. 3.—Barium enema. Absence of physiologic shadow at "A."

we were satisfied that the cecum either could or could not be filled. We only classed those cases as positive which gave an incomplete filling by both methods. With the enema, pressure with the palpating hand fails to keep the barium in the involved portion of the colon. When it is forced in, as soon as the pressure is removed, it rapidly shoots out, the uninvolved portion remaining filled. All patients were examined fluoroscopically and plates were taken as a matter of record.

At Trudeau Sanitarium, Brown and Sampson prefer the barium meal, while Carmen at the Mayo Clinic, on the other hand, prefers the enema, claiming that small filling defects can better be determined by this method. In our work we found no discrepancy in the two methods. Of our 80 cases, 12, or 15 per cent, were positive, showing a definite filling defect in the cecum or ascending colon. In our 4000 non-tuberculous cases we were not always



FIG. 4.—Mouth filling. Filling defect at "A."

able to visualize a completely filled colon, but in each instance there was a definite reason for the failure, like carcinomatous infiltration, adhesions or pressure from a neighboring tumor. Also in achylia gastrica, after a barium meal, in cases associated with diarrhea we encountered a distinct hypermotility, and as a result the barium was forced along so rapidly that a completely filled cecum could not be observed. A contrast enema, however, accomplished this and differentiated the condition from intestinal tuberculosis. We



believe with Stierlin,<sup>11</sup> etc., that the filling defect is the most important roentgen sign of cecal tuberculosis. How much of the deformity is due to infiltration and how much to reflex spasm cannot be determined by the roentgenologist. When marked thickening and contraction have taken place there may be obstruction.

We were surprised by the frequency of gastric hypomotility, barium frequently remaining in the stomach seven and eight hours after the ingestion of the meal. This has a practical bearing on the treatment of pulmonary tuberculosis, as a few years ago forced feeding was considered an essential element for recovery. To force-feed a stomach unable to dispose of an ordinary meal is



FIG. 5.—Mouth filling. Filling defect at "A."

illogical. The overfilled stomach may cause the anorexia, distention and fermentation so frequently complained of, and explains why these patients give up one article of food after another, believing that it is the food eaten at the last meal which causes the disturbance, whereas in reality it is due to the fermentation of the food remaining in the stomach from previous meals that is at fault. The meal must not be greater than the stomach can propel into the small intestine before the next meal is partaken. In our contrast enema studies we were impressed by the frequency of the ileocecal incompetency (25 per cent). In 70 per cent there was a marked ileal stasis. All of our positive cases were sensitive

<sup>11</sup> Loc. cit.

in the cecal region, but in none was a definite tumor palpable. In the symptomatology our patients volunteered the information that they felt weak and prostrated after a bowel movement, and also that the odor of the stool was very foul and penetrating.

In their first report, Brown<sup>12</sup> and Sampson laid considerable stress on hypermotility of the colon as a sign of tuberculous colitis. There is, however, no true hypermotility but rather a rapid passage of the colonic contents through the involved area, due to rigidity of the infiltration or the contraction of the spasm.

It must, however, be borne in mind that roentgenology does not diagnose tuberculosis of the intestines, as the same findings occur in cancer and ulcerative colitis as mentioned by Stierlin.<sup>13</sup> Roentgenology should not be required to make a pathologic diagnosis. This should be reserved for the pathologist. Roentgenology is nothing but inspection, and as such is a part of clinical medicine. Sufficient evidence is now at hand, however, to warrant the inference that a filling defect in the cecum or ascending colon in a person afflicted with tuberculosis and associated with gastrointestinal symptoms is almost always indicative of tuberculosis of this area. We have then in roentgenology a very important aid in the diagnosis of tuberculous colitis. The importance of the early diagnosis cannot be overemphasized, as only then can treatment be of avail. Mild lesions sometimes heal spontaneously. Drugs are of no value. Surgery in the hands of qualified operators has given very satisfactory results. Even in advanced cases the recent reports of Archibald<sup>14</sup> and Patterson<sup>15</sup> emphasize this. Roentgen ray, radium and more recently heliotherapy in the form of the quartz lamplight are being used extensively, the latter especially at Saranac.

We wish to take this occasion to express our thanks to Dr. H. J. Brayton for the privilege of examining the patients at the Onondaga County Tuberculosis Sanitarium, which forms the main basis of this paper.

<sup>12</sup> Loc. cit.

<sup>13</sup> Loc. cit.

<sup>14</sup> Loc. cit.

<sup>15</sup> Intestinal Tuberculosis, *Am. Rev. Tuberc.*, 1920, 4, 433; *Albany Med. Ann.*, 1920, 41, 285.

## REVIEWS.

---

A TEXT-BOOK OF PRACTICAL THERAPEUTICS. By HOBART AMORY HARE, M.D., LL.D., B.Sc., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College of Philadelphia; Physician to the Jefferson Medical College Hospital; one-time Clinical Professor of Diseases of Children in the University of Pennsylvania; Commander U.S.N.R.F. Eighteenth edition. Pp. 1033; 144 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

ALTERATIONS and additions to this well-known work have resulted in a book containing fifteen pages more than the seventeenth edition. The grouping of donors for transfusion is discussed at some length and a detailed description of the method of transfusion with citrated blood is given. A paragraph is devoted to the use of quinidine in auricular fibrillation, silver arsphenamine in syphilis, and thyroxin in cretinism. Directions are given for the preparation of solutions of gum acacia for intravenous use, and the treatment of chronic nephritis is taken up in more detail than in the previous edition.

J. H. A.

A TREATISE ON HYGIENE AND PUBLIC HEALTH. By BIRENDRA NATH GHOSH, F. R. F., PAND S. (GLASG.); F.R.S.M., Examiner in Hygiene and Pharmacology, University of Calcutta, etc., and JAIR LAL DAS, D.P.H., Member of the Royal Sanitary Institute. Fourth edition. Pp. 507; 62 illustrations. Calcutta: Hilton & Company, 1921.

THE twenty-four chapters of this little book are chiefly concerned with the usual topics of water, air, soil, food, climate, sanitation of houses, schools, villages, etc. Although there is a natural undercurrent of the Indian aspects of public health, it affords much of interest to one who is not specializing on this subject. To the specialist there can be little of value, beyond a few local topics, such as Chapter VIII on "Diet in India," occasional sections on malaria, plague and similar diseases, and the local methods of building, personal hygiene and disposal of the dead. Discussion

of the action of alcohol and Pettenkofer's views on the spread of enteric, the omission of such recent developments as the relation of lice to trench fever, etc., indicate that the book has not been kept strictly up to date in successive editions, but the total absence of references make this a difficult matter to estimate accurately. The index also is far from complete. E. B. K.

---

HYGIENE OF WOMEN AND CHILDREN. By JANET E. LANE-CLAY-PON, M.D., D.Sc. (Lond.), Dean and Lecturer on Hygiene in the Household and Social Science Department, King's College for Women. Pp. 339; 71 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

THIS exceedingly interesting book on the hygiene of women and children represents the outgrowth of the gradual development of communal hygiene into the individual practices of such rules and modes of living as are prone to protect and prolong life under the most felicitous circumstances. Such teaching as is found in the book may probably be found in larger specialized volumes elsewhere, but its collection into one volume in an easily read text, copiously illustrated, has not been done previously. One follows in a very logical order through general sanitation to house sanitation, individual hygiene of the woman, mother and infant, with chapters interspersed on such subjects as the collection and storage of foods, beverages, milk, artificial feeding, notes on rickets and scurvy, and the care of young children. All this information is in a simple and practical form which should make the book an invaluable manual for the use of the sanitary inspector, the visiting nurse, the teacher, and it may be thoroughly recommended, in addition, as a book to be placed in the hands of parents and any one whose activities are devoted to the betterment of the living conditions of women and children. P. F. W.

---

STUDIES IN PALÆOPATHOLOGY. By SIR MARC ARMAND RUFFER, M.D., Late President of the Quarantine Council of Egypt, etc. Edited by ROY L. MOODIE, Ph.D., Associate Professor of Anatomy in the University of Illinois. Pp. 372; 71 plates. University of Chicago Press, Chicago, 1921.

THE term palæopathology was first used in medical literature by the author of these studies, to describe the subject to which he has made such interesting and valuable contributions. He defines it as the science of the diseases which can be demonstrated in

human and animal remains of ancient times. The greater part of the work was done in Egypt, where he served for many years (1901-17) as president of the Sanitary Council. He began by preparing microscopic sections of various parts of mummies. Only after many experiments was he able to get the tissues to the right degree of consistency for embedding in paraffin, cutting on a rotary microtome and staining. In such histological sections he could recognize the cross striations of voluntary muscle fibers from subjects three thousand years old. The main characteristics of bloodvessels, of nerves and of the heart were surprisingly well preserved. The microscopic specimens thus prepared varied greatly in the amount of detail which they showed, and this fact probably depended chiefly on the original method of preservation of the bodies, whether by some method of embalming or by simple drying. In favorable preparations he could identify the layers of the skin, the glomeruli and tubules of the kidney, the coats of intestine, as well as liver, bone, and other structures. He then in a similar way studied pathological lesions in more ancient mummies, some as old as eight thousand years. Here he found atheromata of the aorta and of other arteries; in different specimens of lungs, he saw anthracosis, hepatization of pneumonia and numerous bacilli; in kidneys, he found multiple abscesses with well-staining bacilli, and in two mummies of the twentieth dynasty (1250-1000 B.C.), he found numerous eggs of *Bilharzia hæmatobia*. He continued his studies of arteriosclerosis. The etiology of this condition he considers very obscure, as no tobacco was smoked and alcohol was not used to excess. In support of his theory that alcohol had not necessarily anything to do with the condition, he quotes his own experience of having made during the Mussulman pilgrimages, over eight hundred postmortems on people who had certainly never touched alcohol during their lives, and he found the condition just as common in them as in people who take alcohol regularly. He described a case resembling smallpox, but the pathological evidence is not convincing. Diseases of the bones and teeth show themselves distinctly and in several forms. No syphilitic bones or teeth were ever observed. However, arthritis deformans, spondylitis, tuberculous lesions, bony tumor of pelvis and lesions of pyorrhea alveolaris were found. This book will appeal to all pathologists and to a certain number of antiquarians. In it the researches of science link the distant ages of early Egypt with the present day in disease, in malformation and in suffering. That the study of the mummies should reveal all this is not surprising, but that the perseverance and enthusiasm of man should accomplish this study is more a matter for wonder. The illustrations add greatly to the vividness of the subject, and a chronological appendix is valuable for localizing the ages of the various remains.

W. H. F. A.

THE HEART RHYTHMS. By PAUL DUDLEY LAMSON, M.D., Associate Professor of Pharmacology, Johns Hopkins University. Pp. 98; 52 illustrations. Baltimore: Williams and Wilkins Company, 1921.

THIS valuable little book deals with the cardiac arrhythmias in a concise, logical and readable manner. No attempt is made to present any new observations, nor are symptomatology or treatment discussed. The work deals almost exclusively with the mechanism and recognition of normal and abnormal rhythms. Noteworthy points in the author's treatment of the subject are his classification of rhythms according to the point of origin of the contraction impulse, and the diagrammatic division of the heart into four functional areas. The characteristic electrocardiographic complex of each area is shown, together with the rhythms which may result from the contraction impulse originating here. The chapter upon the interpretation of the electrocardiograph might with advantage have been made more complete, yet sufficient is said to aid the beginner in interpreting tracings, and not enough to confuse. The polygraph and sphygmograph are discussed at greater length and the directions for making and interpreting polygraphic tracings are given with admirable clarity. The author feels that since through the electrocardiograph the whole subject of the cardiac rhythms has been clarified, and the interpretation of polygraphic tracings put upon a more scientific basis, it is now time for the polygraph to come into more universal use with the general practitioner who needs such a compact, portable, and relatively inexpensive instrument rather than the electrocardiograph. The book is well worth reading, and will appeal especially to students and teachers of cardiology as well as to the general practitioner.

J. H. A.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Professor of Diseases of the Skin, University of Kansas School of Medicine; Former Chairman of the Dermatological Section of the American Medical Association; Assistant Surgeon, United States Navy, Retired; Dermatologist to the Christian Church Hospital. Fourth edition. Pp. 1132; 969 illustrations. St. Louis: C. V. Mosby Company, 1921.

THE present fourth edition of Sutton's *Diseases of the Skin* is larger by forty-eight pages than its predecessor, and the total number of illustrations are increased by fifty-nine over the previous edition. Syphilis along its various lines has been amplified. The progress made in the study of the various fungus diseases is recorded in greater detail. Various dermatological conditions such as no-

cardiosis, Vincent's disease, dermatitis dysmenorrhoeica, amebiasis cutis, and neurotic excoriations of the skin have been transferred to new headings. The readers of the volume who wish to carry their investigations further will be assisted by the six hundred and forty additional references to dermatological literature. The present edition carries out the wishes of the writer in regard to practical treatment and amplification of cutaneous pathology. The profusion of excellent illustrations makes the volume virtually an atlas in addition to a text-book. The reviewer believes that there is no better American text-book today on dermatology than Sutton's excellent volume.

F. C. K.

---

DISEASES OF THE SKIN. By HENRY W. STELWAGON, M.D., Ph.D., Late Professor of Dermatology in the Jefferson Medical College; Late Consultant to the Dermatological Department of the Philadelphia General Hospital; to the Howard Hospital; to the Pennsylvania Institution for the Deaf and Dumb; to the Pennsylvania Institution for Feeble-minded Children; and to the Widener Memorial Training School for Crippled Children; Late Member of the American Dermatological Association; Late Honorary Member of the Society of Dermatology and Syphilography of Italy; Late Associate Member of the Society of Dermatology and Syphilography of France; of the Vienna Dermatological Society, and of the Berlin Dermatological Society; and HENRY KENNEDY GASKILL, M.D., Attending Dermatologist to the Philadelphia General Hospital and Member of the American Dermatological Association. Ninth edition. Pp. 1313; 401 text-illustrations and 29 colored and half-tone plates. Philadelphia and London: W. B. Saunders Company, 1921.

THE last edition, the eighth, of Dr. Stelwagon's excellent book *Diseases of the Skin*, appeared in October, 1916, and the present edition, the ninth, is dated July, 1921. Owing to the death of Dr. Stelwagon, in October, 1919, a change in authorship proved necessary and the preparation of the present edition was placed in the capable hands of Dr. Henry K. Gaskill. It is always a difficult matter to carry out the ideas and style of an originator and the present author has succeeded admirably in effacing himself and bringing before the public the idea that this is the dermatological treatise of Dr. Stelwagon rather than the present compiler. According to the author, "A great part of the value in Dr. Stelwagon's treatise lies in his meticulous search for references," and many additional articles are quoted in the text and mentioned in footnotes in the present work. Various new conditions of the skin are described, such as acrodermatitis hiemalis, endothelioma, espundia, keratolysis

exfoliativa, amebiasis cutis, and folliculitis ulerythematososa reticulata. Seventy-four new illustrations have been added and a few of those formerly employed have been eliminated. The volume still maintains the excellence of former editions.

F. C. K.

---

SYNOPSIS OF MIDWIFERY. By ALECK W. BOURNE, B.A., M.B., B.Ch. (Camb.), F.R.C.S., (Eng.), Obstetric Surgeon to In-Patients, Queen Charlotte's Hospital; etc. Second edition. Pp. 295; New York: William Wood & Company, 1921.

THIS small volume is frankly intended for a means of rapidly reviewing obstetrics in case of a student or practitioner brushing up for final collegiate or licence examinations. The preface states that in this, the second, edition there have been some changes in the subjects of toxemias of pregnancy and hemorrhages. The abridgment of the subject-matter has been well done. The next presents the essentials of obstetrics in crisp, concise sentences. There is no discussion, and a middle-of-the-road attitude is taken in disputed points. The book is a good manual for a rapid *resume* of the subject.

P. F. W.

---

NUTRITION AND GROWTH IN CHILDREN. By WILLIAM R. P. EMERSON, Professor of Pediatrics, Tufts Medical College. Pp. 342; 56 illustrations. New York and London: D. Appleton & Company, 1922.

THE writings of the author upon the subjects of nutrition and growth are well known. Many of his papers have appeared in medical literature and not a few in magazines devoted to circulation among the laity. In the present volume will be found a complete and practical survey of Dr. Emerson's work. It would seem that this book is intended for use for parents, teachers and social workers as well as for medical men. In the preface one finds mention of the first nutrition class which was organized in 1908 by Dr. Emerson at the Boston Dispensary. From this beginning the work has spread so that the present time sees special clinics and classes throughout the country, all of which are modelled to a large extent along the lines which are clearly set forth in the book under discussion. The twenty-eight chapters are presented in three sections—the diagnosis of malnutrition, malnutrition and the home, a nutrition program for the community. The underlying principle set forth is that there are five chief causes of malnutrition which must be looked for and corrected. In order of importance these are—physical defects,



especially nasopharyngeal obstructions; lack of home control; overfatigue; improper diet and faulty food habits; faulty health habits. It will be noted that improper diet comes fourth on the list and this position is well supported by the arguments presented. In the diagnosis of malnutrition the relation of weight to height is taken as an accurate standard. It should be mentioned that the illustrations are excellent and to the point.

A. G. M.

**TUMORS, INNOCENT AND MALIGNANT.** By SIR JOHN BLAND-SUTTON, L.D., F.R.C.S., Consulting Surgeon to the Middlesex Hospital. Seventh edition. Pp. 806; 383 illustrations. New York: Paul B. Hoeber, 1922.

THE medical profession should by this time be so well acquainted with this important book that little comment is needed upon the appearance of a new edition. Though "old fashioned" in its presentation of the subject, in the character of its illustrations and in its comparative neglect of histological details, it nevertheless continues to be of value to physician, surgeon and pathologist alike, on account of its wealth of illustrative material and case reports and the sound judgment of the thoughtful and experienced author. Almost half the references are to publications of the preceding century. Exception might be taken to various details of tumor classification and prognosis, but with the present lack of agreement on these topics this could hardly be otherwise. Radiotherapy is given but scant attention, so that one is not surprised to find lukewarm and rather vague recommendations that were more frequent in the previous decade than at present. Also one is forced to disagree with the statement on page 281 that "it is impossible without injury to the skin to administer a sufficiently strong exposure to influence malignant tumors of the viscera." A list of illustrations in this book is especially needed. The use in the index of black-face type for the main items is a detail well worth publishers' attention.

E. B. K.

**CLINICAL ELECTROCARDIOGRAPHY.** By FREDERICK A. WILLIUS, B.S., M.D., M.S. in Medicine, Section on Clinical Electrocardiography, the Mayo Clinic, Rochester, Minnesota, and the Mayo Foundation, University of Minnesota. Pp. 188; 185 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

To the reviewer it would appear that this book has a number of serious faults and is not up to the high standard set by other works

on clinical electrocardiography. One-sided statements of debatable points are made (as in the discussion regarding the significance of the T-wave). The classification of abnormal cardiac mechanisms is artificial and has no advantages that are apparent. The description of auricular flutter as an acceleration of the auricles to a rate beyond 200 a minute, reveals how remarkably little the author has been influenced by the recent work of Lewis on this subject. A number of the tracings (Figures 48, 52, 57, 60 and 64) are susceptible of interpretations other than those ascribed by the author, while in Figures 54, 58, 62 and 76, errors in interpretation are noted.

On the credit side may be placed the follow-up statistics of patients who had shown various abnormalities in their electrocardiograms and the excellent collection of tracings of patients with angina pectoris.

C. C. W.

THE PLACE OF VERSION IN OBSTETRICS. By IRVING W. POTTER, M.D., F.A.C.S., Obstetrician to the Deaconess, St. Mary's, City, Columbus, Homeopathic and Salvation Army Hospitals of Buffalo. Pp. 133; 42 illustrations. St. Louis: C. V. Mosby Company, 1922.

WHETHER the place of version in obstetrics is or is not to be made the routine method of delivery of all cases capable of being delivered by the natural passages rests upon the personal convictions of the individual operator. Potter believes the form of version which he has perfected should supplant the mechanism of normal labor. This excellently illustrated monograph, which may be studied with profit, is a very clear and detailed exposition of the Potter version.

P. F. W.

THE CLINICAL STUDY OF THE EARLY SYMPTOMS AND TREATMENT OF CIRCULATORY DISEASE IN GENERAL PRACTICE. By R. McNAIR WILSON, M.B., CH.B., late assistant to SIR JAMES MACKENZIE under Medical Research Committee; late Cardiologist, War Office Trench Fever Committee; Consulting Physician, Ministry of Pensions. Pp. 245; 111 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

THE book commences with a brief foreword by Sir James Mackenzie. An introduction then expounds the author's main hypothesis, namely, that stimulation of the vagus may reflexly stimulate the sympathetic and thus lead to a sympathetic reaction, the end result being quickening of the pulse instead of the expected slowing.

Observations made by the author upon himself, his friends, his patients and soldiers suffering from trench fever are then invoked

in abundance to prove his hypothesis and to emphasize the importance of such factors as intestinal stasis, improper breathing and toxin states in producing certain morbid conditions. These morbid conditions are described largely in terms of vagus or sympathetic activity and include breathlessness, cyanosis, exhaustion, headache, hyperalgesia, pain, tachycardia, fever and other similar conditions. The book abounds in repetitions, and one feels after reading it that one has accompanied the author through many tedious observations and explanations, but carried away very little of value regarding the early symptoms and treatment of circulatory disease in general practice.

J. H. A.

LEHRBUCH DER GRENZGEBIETE DER MEDIZIN UND ZAHNHEILKUNDE.

By JULIUS MISCH, dentist, Berlin, with the collaboration of a number of physicians. Second edition. Two volumes, pp. 1363; 351 illustrations. Leipzig: F. C. W. Vogel, 1922.

THIS book is stated to be for students, dentists and physicians. The various sections of the book are written by physicians in conjunction with Dr. Misch and apparently the effort has been made to present the subject-matter from the viewpoints both of physicians and dentists. The oral and particularly the dental manifestations of the various ills the body is heir to are exhaustively discussed, as well as the general effects of disorders of the teeth. The many illustrations, for the most part, are excellent.

There has been real need for a book of this sort and it has already enjoyed a deserved popularity in Germany. Its usefulness could be increased by the elimination of a great deal of unnecessarily lengthy discussion of the diagnosis and treatment of systemic diseases.

C. C. W.

SURGICAL CLINICS OF NORTH AMERICA. VOL. I, No. 6 (NEW YORK NUMBER). Pp. 295; 122 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

THIS number of the Clinics is an especially interesting one, taking up, as it does, thoracic surgery, cord surgery, some features of abdominal surgery and miscellaneous subjects. The contributors are all men well known in their line and in most instances the subjects chosen by them for this publication express the direction of their chief accomplishments. For this reason the reader probably gets the very best data on that particular condition and its treatment.

It is exceedingly interesting and instructive reading and shows very well the steady improvement and advance in surgical diagnosis and technic.

E. L. E.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**Hemosiderosis of Pernicious Anemia.**—McMASTER, ROUS and LARIMORE (*Jour. Exp. Med.*, 1922, 25, 521) point out that in recent years pernicious anemia has been thought by many to be due to an injurious agent derived from the gastro-intestinal tract. One of the findings which has been considered well-nigh conclusive in support of this idea is the marked siderosis of the liver parenchyma, which has been taken to indicate that pathological blood destruction is localized within the portal tributaries. They show experimentally that this hemosiderosis is inconclusive evidence of blood destruction within the portal system. Young rabbits were injected subcutaneously with varying amounts of rabbit hemoglobin on six days out of every seven. The injection periods ranged from thirteen to one hundred and two days, the hemoglobin dose from  $\frac{1}{4}$  of that normally possessed by the animal to  $\frac{1}{150}$  of it. The liver, kidneys, spleen and red bone marrow were studied with reference to their hemosiderin content. The following results were obtained. The distribution of the hemosiderin depended on the amount of hemoglobin given. No siderosis occurred when a daily portion less than  $\frac{1}{30}$  was employed. When slightly larger doses were used over long periods of time a siderosis of the liver occurred, similar to that in pernicious anemia, whereas the kidneys were non-pigmented or negligibly so. When more hemoglobin was used the differences in the organs became less noteworthy and when very large injections were given resulting in hemoglobinuria after but a few days, the epithelium of the renal tubules was heavily pigmented and the liver cells by con-

trast negligibly so. In these experiments they show that the constant presence in the general, as distinct from the specifically portal, circulation of a small amount of free hemoglobin, leads eventually to a siderosis of the liver similar to that which has been considered so significant in pernicious anemia. When this amount is kept within certain limits, renal siderosis fails to appear or is negligible in degree. When more is given the epithelium of the renal tubules rapidly becomes pigmented, the iron deposition far outstripping that in the liver. Their conception of the phenomenon is that the liver is able to remove free hemoglobin from the blood stream, and normally is probably the organ which keeps the plasma free of hemoglobin. When the hemoglobin coming to it is increased, it may still receive it but in so doing become siderosed. When hemolysis is considerable the liver is overtaxed and the pigment accumulates in the blood and is dealt with by the kidneys according to its threshold of excretion. The hemosiderin passes readily through the glomeruli but undergoes a greater or less resorption during its passage through the tubules and renal siderosis comes about. They believe that the variations in distribution of hemosiderin in pernicious anemia are rendered understandable by these facts.

---

**Tularemia Francis 1921.** A New Disease of Man.—FRANCIS' (*Jour. Am. Med. Assn.*, 1922, 78, 1015) report has to do with one of a series of most important observations which have been carried on by McCoy and his associates of the United States Public Health Service, the impetus for which was received during the fight against plague in California in 1911. At that time McCoy recognized a plague-like disease of rodents, which was differentiated from true plague, and of which tularemia was later found to be the etiological agent. This plague-like disease has been found in squirrels, rabbits and guinea-pigs, being transmitted by various insects. Of importance to the profession is the discovery that this disease occurs in man from sources of infection in California, Indiana and Utah and that it is readily contracted by laboratory workers intimately associated with experimental work upon this infection. When the disease is contracted by insect bite it is characterized by a well-marked reaction at the site of infection, which is followed after a brief incubation by lymphadenitis of the regional glands, chills and fever and prostration for a period of from one to four weeks. Laboratory workers contracted the disease without obvious sites of infection; they all showed a sudden onset of fever, without other definite manifestations, which lasted with remissions about three weeks. All of the trained workers of the service who were immediately concerned with the investigation had the infection and showed characteristic immunological reactions. Francis points out that "the ready susceptibility of man to this infection in Nature and in the laboratory, its wide prevalence in Nature in a number of rodents, and the growing number of blood-sucking insects found capable of conveying the infection, should combine to put the medical profession of the United States on the watch for cases of this new disease of man."

---

**Length of Life of Transfused Erythrocytes.**—WEARN and his co-workers (*Arch. Int. Med.*, 1922, 29, 527), using the technic devised by Ashby determined the duration of the existence of Group IV trans-

fused red blood corpuscles in the circulation of patients whose blood belonged to Group II. Four cases of pernicious anemia and four of anemia secondary to nephritis were studied. The last of the transfused red blood cells disappeared from the circulation in from fifty-nine to one hundred and thirteen days, with an average of eighty-three days. No difference was noted between the duration of the stay of the transfused cells in the circulation of patient with primary and secondary anemia. One of the cases of pernicious anemia (Group II) was transfused with blood from another case of pernicious anemia (Group IV) and in this instance the transfused cells behaved as did the corpuscles from normal donors.

---

## SURGERY

---

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

---

**A Consideration of the Relative Merits of Resection and Gastro-enterostomy in the Treatment of Gastric and Duodenal Ulcer.**—DE QUERVAIN (*Surg. Gynec. and Obstet.*, 1922, 34, 1) says that he has abandoned schematic gastro-enterostomy and leans more toward resection. Ninety per cent of ulcer recurrencees, peptic ulcer and other disturbances, occur in the first four years after operation, so that statistics which depend on results reported earlier are apt to show too favorable results. Simple gastro-enterostomy produces in all forms of gastric ulcer about the same early results—somewhat more than four-fifths cure or improvement approximating cure. In ulcers at a distance from the pylorus the average results are no less favorable than in those at the pylorus. With sleeve resection, there is no late bleeding from the ulcer with the resultant occasional death and the danger from peptic ulcer is almost *nil*.

---

**Benign Tumors of the Stomach.**—EUSTERMAN and SENTY (*Surg. Gynec. and Obstet.*, 1922, 35, 5) say that benign tumors of the stomach are rare and constitute only 1.3 per cent of all gastric tumors that have come to operation. The actual proportion of benign new growths to malignant new growths or ulcerations is as 1 to 200. Myomata and fibromata constitute the largest group, gastric polyposis the most infrequent. About 50 per cent of benign tumors are found in patients more than forty years old. There is no characteristic syndrome and gastric chemism ranges from achylia to hyperacidity with hypersecretion. The summation of evidence favors the diagnosis of gastric cancer. The majority of tumors are situated in the region of the pylorus, the greater curvature, anterior and posterior walls. The smaller tumors are

practically symptomless unless situated at the orifices or unless multiple. Common complications are recurring hemorrhage and pyloric obstruction. Palpable mass and food retention are less frequent than in gastric cancer.

---

**Essential Hematuria.**—LEVY (*Surg. Gynec. and Obstet.*, 1922, 34, 22) says that the diagnosis of essential hematuria should be made only when all known urological methods have been employed with negative findings for it is purely a clinical diagnosis indicating renal bleeding of unknown etiology. In 36 per cent of the cases, the onset of the hematuria occurred in the fourth decade of life. The bleeding developed spontaneously in most cases and was symptomless. The right kidney was responsible for the bleeding in 17 cases and the left in 13. In no case were both kidneys involved. The results of operative procedures have not been better than those of non-operative methods. In the author's series, there were recurrences after decapsulation and two nephrotomies. Nephrectomy is the only operation ever indicated and that only as an emergency measure to save a patient from bleeding to death. Non-operative methods have been used with success, including intrapelvic injection of silver nitrate and adrenalin, the oral administration of calcium lactate and the subcutaneous or intramuscular injection of horse serum. Spontaneous cessation of the bleeding occurs frequently in essential hematuria.

---

**Results in One Hundred Cases of Cancer of Prostate and Seminal Vesicles, Treated with Radium.**—DEMING (*Surg. Gynec. and Obstet.*, 1922, 34, 99) says that a combination of radium and surgery offers a possibility for treatment of cancer of the prostate and seminal vesicles. While operation does not diminish the amount of radium necessary to produce good results it does not increase the possibility of hastening metastases. Radium gave symptomatic relief and return of normal urination in 75 per cent of the cases. Moreover, radium relieved the pain in the back in 50 per cent of cases suffering from metastases. Irritation from radium can be avoided by treating widely remote areas in successive treatments and by alternating between rectal, urethral and vesical applications. At least 3000 milligram hours must be given to produce symptomatic and local results in the same patient. Cases which did not respond to radium did not receive sufficient radiation. Large doses must be given in as short a period as possible to produce maximum results. Combined extraglandular and intraglandular radiations apparently give the most satisfactory results.

---

**Synovial Membrane Tumors of Joints.**—HARTMAN (*Surg. Gynec. and Obstet.*, 1922, 34, 161) says that the occurrence of this type of tumor in joints and especially in the knee-joint raises at once the problem of saving the limb and the function of the joint. Their development is slow as a rule and ample warning is always given in the form of pain, swelling and interference with function. They are readily removed if attacked in the early pedunculated stage without danger of local recurrence or remote metastases. For classification, it seems best to place them with the benign tumors of connective tissue origin since the giant cells are of the foreign body type and no mitosis is seen. There is however a

potential malignancy. Palliative measures and incomplete excision are contraindicated and are perhaps responsible for the malignant characteristics developed in these cases. These neoplasms should not be termed sarcoma at least until evidences of malignancy are seen either clinically or pathologically. Since any one of the characteristic cells, namely xanthoma or foam cells, pigmented cells and giant cells, may be absent from an otherwise typical case the writer prefers the name of myeloid tumor.

---

**Carcinoma of Prostate.**—BARRINGER (*Surg. Gynec. and Obstet.*, 1922, 34, 175) says that in but 2 per cent of cases of carcinoma of the prostate seen at the Memorial Hospital, is the carcinoma confined to the prostate. Routine prostatic examination of all patients beyond the age of fifty, irrespective of symptoms is the only rational method whereby we may hope to make a diagnosis of prostatic carcinoma early in the disease. The results of radium treatment of carcinoma of the prostate are superior to operative removal both in causing regression of the disease and in coping with urinary retention.

---

**Thyrotoxicosis.**—BLACKFORD (*Surg. Gynec. and Obstet.*, 1922, 34, 185) says that there are two points to be emphasized, importance of early diagnosis in order to obtain a cure by surgical removal of a toxic goiter before permanent damage is done the patient. The mortality from removal of non-toxic or mildly toxic cases is almost zero in competent hands. Second, a badly damaged heart from goiter intoxication does not contraindicate surgery. Practically speaking, the cardiac reserve of the patient can be improved by treatment until good enough to withstand operation. The bulk of surgical mortality occurs in badly toxic cases, not in the extreme cardiopaths.

---

**Histology and Mortality in Cases of Tumor of the Bladder.**—SCHOLL (*Surg. Gynec. and Obstet.*, 1922, 34, 189) says that 41 per cent of all patients operated on for malignant papillomata are alive on an average of three years after operation while only 11 per cent of patients with solid carcinoma have lived more than three years after operation. The incidence of recurrence following operation on patients for solid carcinoma is much greater than that for malignant papillomata. Squamous-cell carcinomata of the bladder are extremely malignant and rapidly fatal while adenocarcinomata are about as severely malignant as papillomata. Simple angiomas of the bladder may grow so large as to cause obstruction. Myomata of bladder often grow very large. Myxomata occur generally in young persons. Sarcoma is probably the rarest and most malignant of vesical tumors. It occurs in middle-aged persons, metastasizing extensively with tendency to rapid recurrence.

---

**Duodenal Ulcer in Infancy.**—PATERSON (*Lancet*, January 14, 1922, p. 63) says that duodenal ulcer is a rare condition in infants but more careful examination of the duodenum in marasmic infants may show it to be more common than is at present admitted. Ulcers may be present in melena neonatorum. In older infants, they may follow on any gastro-intestinal upset. They may certainly complicate extensive septic burns or septicemia. Tuberculosis is the common cause of



duodenal ulcers in older children. The diagnosis of duodenal ulcer is difficult and usually not made. Duodenal ulcer may be successfully treated by operation.

---

**Ulcer of Lesser Curvature of Stomach.**—FABER (*Lancet*, January 14, 1922, p. 65) says that gastric ulcer in the corpus of the stomach (on the lesser curvature) is commoner in women than in men. Juxtapyloric ulcer is more frequent in men than in women. Gastric ulcers are chiefly ulcers of the corpus in women, and juxtapyloric ulcers in men. Statistics of postmortem examinations show that gastric ulcer is commoner in women than in men. Ulcer of the corpus may therefore be assumed to be the more frequent variety. On account of their symptoms and course, juxtapyloric ulcers make easier subjects for surgical treatment than ulcers of the corpus. For this reason, statistics of operative material so often show a preponderance of men. Ulcer of the corpus, which might be called the women's ulcer, has a more favorable course than the juxtapyloric. It heals more readily and the raw ulcer found postmortem has more often than the juxtapyloric, the character of a fresh acute ulcer. Ulcer of the corpus often lacks the symptom-complex so characteristic of the juxtapyloric ulcer, especially the late pains and the hypersecretion. This obtains in the case of recent and chronic ulcer of the corpus. We may presume that a large number of ulcers of the corpus as a rule in women make their appearance and get well again without the diagnosis "gastric ulcer" being made.

---

**Neurofibromyoxoma Treated by Conservative Operation.**—GATCH and RITCHEY (*Ann. Surg.*, 1922, 75, 181) say that various authors believe that benign fibrous or fibromyxomatous tumors of nerve sheaths may undergo malignant degeneration into sarcoma. If the tumor is of long duration, it is not likely to be malignant. The presence or absence of motor or sensory paralysis is a most valuable point. A nerve will withstand a really remarkable amount of stretching or pulling from a benign growth but is quickly destroyed by the infiltration of its substance by a sarcoma. The gross appearance is significant. The encapsulation of the fibrous portion of the tumor and the possibility of shelling the same from the center of a nerve trunk would seem to be strong evidence of a benign growth, as is the lack of encapsulation with fixation of the growth to the contiguous structures strong evidence for sarcoma. The authors feel that microscopic study to the exclusion of other factors is misleading.

---

**Ruptured Spleen.**—METCALFE and FLETCHER (*Ann. Surg.*, 1922, 75, 186) say that the healthy spleen may rupture spontaneously or from comparatively slight trauma. The symptoms at first may be slight; some dizziness, nausea or vomiting with restlessness and indefinite abdominal pains or the immediate symptoms may be severe intra-abdominal hemorrhage depending upon this contingency whether the capsule of the spleen has ruptured or remained intact, forming a large subcapsular hematoma. In the authors' cases an agonizing pain was felt in the left shoulder. They feel that it is of value in diagnosis with evidence of hemorrhage. They advocate immediate splenectomy as the only safe treatment.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**Studies of Infant Feeding—A Bacteriological Study of the Feces and the Food of Normal Babies Receiving Breast Milk.**—BROWN and BOWORTH (*Am. Jour. Dis. Children*, 1922, 23, 243) found that direct smears from the stools of normal breast-fed babies present a practically constant picture, which is characterized by an almost complete dominance of the bifidus group. In this picture cocci and Gram-negative organisms are indistinguishable or are present in very small numbers. This proportion of bacterial types may be changed by abnormal physiologic conditions. A baby who has been on cow's milk formula for several days, although originally breast-fed, may show bacteriologically the effects of this diet even as long as four weeks after the continuous ingestion of breast milk. This is indicated from the smears from the feces by a larger number of cocci and Gram-negative bacilli than is typically found as characteristic of a normal breast-milk stool. If a cow's milk formula is used before the third day after birth, and breast milk is used thereafter, the establishment of fecal types of bacteria follows the course of the normal nursling very closely. From the study of anaërobic cultures it was found that *B. bifidus* is also the dominant living type of organism in the feces of normal breast-fed infants. The proportion of types represented in the direct smears is closely paralleled by the proportion of types growing on anaërobic cultures. Aërobic cultures from the feces of normal nurslings typically showed a predominance of colon-aërogenes groups. This may be lessened by abnormal physiologic conditions. While the study of the fecal flora of infants by anaërobic culture seems to be of great importance, aërobic cultures should also be used as a check to determine the presence of aërobic pathogenic bacteria or of adventitious bacteria. The results obtained from the study of drawn breast milk used for supplementary bottle feedings were inclusive, since no definite relationship could be established between the types of fecal bacteria and the bacteria isolated from the milk. This was made more difficult because the babies had not had a monotonous diet which could be used as a check and because the majority of the organisms isolated from the milk were staphylococci and *B. coli*, which may be isolated from the normal stool. This study emphasized the fact that even a slight amount of handling may introduce types of bacteria into the feedings of a bottle-fed baby which a breast-fed infant would not ordinarily ingest. The study of the stools of normal breast-fed babies has shown that a typical monotonous flora in the feces follows the continuous ingestion of breast milk. From the examination of the breast milk it would seem that staphylococci may be ingested in all cases and that a lactic acid bacillus typical of *B. bifidus* may be frequently present in the milk as it comes from the breast. An important

question arises as to the identity of the bifidus-like bacillus which has been isolated from the breast milk and from the skin around the nipple. They think that it is *B. bifidus* and they believe that this group of organisms which are present in or on the nipples of the mother are an important source of the bifidus organisms found in the nursing's intestinal tract.

---

**The Bacteriology of the Normal Infant's Urine.**—HELMHOLTZ and MILLIKIN (*Am. Jour. Dis. Children*, 1922, 23, 309) studied the urine of 75 infants, 35 boys and 35 girls. The results of their studies emphasize the futility of obtaining evidence by the method of Langer and Soldin that in any way will help to settle the problem of the mode of infection in pyelitis. The error that creeps in by contamination, even when all precautions are taken, is such that the evidence obtained is always open to criticism. Their data show that in  $\frac{2}{3}$  of the specimens obtained the urine was sterile, and  $\frac{2}{3}$  of these observations were made in duplicate. They do not agree with Kleinschmidt that at each catheterization a different flora is obtained, nor with Langer and Soldin that a sterile specimen is only an accident, and that repeated catheterization will always yield bacteria in the urine. Recatheterization was repeatedly done and identical results both with regard to sterility and flora were obtained. They call attention to the types of organisms found by Kleinschmidt and by Langer and Soldin, those of the colon group and *Streptococcus lacticus*, which are all inhabitants of the intestinal canal and not normally present in the urethra as far as can be learned. Kleinschmidt asserts that by taking smears from the meatus after cleansing it he was able to prove the constant presence of an organism of the same type as that found in cultures of the urine. The method used by Langer and Soldin of obtaining cultures is also open to criticism since by washing out the urethra, organisms may be easily washed into the bladder. They found long chains of streptococci, which they believed to have grown from organisms coming from the kidney. The most plausible interpretation is that they were washed in from the urethral opening, and are essentially contaminations, as it is not likely that organisms would grow so rapidly in urine and not grow in more favorable culture media after inoculation. The findings of the authors are at variance with those of both Kleinschmidt and of Langer and Soldin in the frequency of occurrence of *Streptococcus lacticus*, which was always present in their cultures. They found it in only 6 instances, and it may have been present in 5 others, so that at most it was present in 15 per cent of the urines examined. In 6 of 11 instances the *Streptococcus lacticus* was found in the liquid medium and not recovered on the solid medium.

---

**Studies of Infant Feeding: A Bacterio-chemical Study of the Acid Stools Excreted by Breast-fed and Bottle-fed Infants.**—BOSWORTH, WILDER, BLANCHARD, BROWN and McCANN (*Am. Jour. Dis. Children*, 1922, 23, 309) describe a method for the distillation of volatile acids from the stools of infants, and also give a graphic method for the study of the nature of the volatile acids, which may be distilled by their technic. Following these procedures they have found that the stools from normal, healthy breast-fed babies are acid in reaction and contain

the volatile acids, formic and acetic. By the same technic they have found that the stools from normal healthy bottle-fed babies are acid, neutral or alkaline in reaction. The acid stools may contain very large amounts of acid and the volatile acid present is acetic acid. *Bacillus aërogenes*, *Micrococcus ovalis*, *Bacillus bifidus* and other unidentified organisms isolated from acid stools possess the power of reducing citrate to a volatile acid. The volatile acid produced by *Bacillus aërogenes*, *Micrococcus ovalis* and other unidentified bacteria was determined to be acetic acid. The volatile acid produced by *Bacillus bifidus* was found to be a mixture of acetic and formic acids. Other organisms like *Bacillus coli*, *Bacillus capsulatus*, *Bacillus acidi lactici*, and *Bacillus cloacæ* disposed of the citrate, producing carbon dioxide and water without the formation of acetic acid. If a synthetic food containing no citrate was fed to an infant, no acetic acid appeared in the stools. If a synthetic food containing a soluble citrate such as sodium citrate was fed, a small amount of acetic acid was found in the stools. If a synthetic food containing an insoluble citrate such as calcium citrate was fed, a large amount of acetic acid was found in the stools. The addition of soluble citrates such as sodium citrate and orange juice to modified milk formulas increased only slightly the acetic acid content of the stools. The addition of an insoluble citrate such as calcium citrate to modified milk formulas resulted in a marked increase in the acetic acid content of the stools. The stools from infants receiving Dryco dry milk contained large amounts of acetic acid. This was probably due to the fact that a considerable portion of the soluble citrate, originally present in the milk, was converted to insoluble citrate during the process of drying.

---

**Potential Heart Disease and Prevention of Organic Heart Disease in Children.**—ST. LAWRENCE (*Jour. Am. Med. Assn.*, 1922, 78, 947) studied 65 cases of potential heart disease for an average period of four and a half years. Forty-nine patients or 75 per cent remained free from evidence of cardiac disease during that time. Of 25 patients with acute rheumatic fever in this series, none contracted a lesion in the heart. Of 9 patients with myositis, bone and joint pains, the so-called growing pains and sore throat, none contracted a lesion of the heart. Sixteen patients or 25 per cent contracted a cardiac lesion while under observation. In every case in which a cardiac lesion developed the clinical picture was dominated by chorea in a severe form. No patient developed a cardiac lesion in the absence of this complication. Of 41 patients with chorea in this series 16 or 39 per cent contracted a lesion in the heart. Measures of value in preventing disease of the heart are of greatest benefit when directed against acute rheumatic fever, myositis, bone and joint pains, the so-called growing pains and sore throat. Such measures have little or no value when directed against chorea. In untreated potential cases, acute rheumatic fever is the most important factor concerning disease in the heart. With the exception of mild mitral stenosis, cardiac lesions practically always occur during the active phase of a rheumatic manifestation or a period of pyrexia. In the absence of an active phase, the physical signs in the heart remain unchanged. Evidence of mitral stenosis may not appear for a year or more after the cessation of the rheumatic manifestations. It is there-

fore impossible to state at the conclusion of an attack of acute rheumatic fever or chorea that the heart was unaffected by those conditions. Heart rate may have a marked effect upon the physical signs of mitral stenosis as shown in graphic records.

---

• **The Function of the Colostrum.**—LEWIS and WELLS (*Jour. Am. Med. Assn.*, 1922, 78, 863) found that the blood of newborn infants, and probably of all other mammals, contains little or none of the serum protein or protein fraction known as euglobulin. This seems to be supplied chiefly by the colostrum, which differs from milk in containing a large amount of this protein secreted directly from the blood. Euglobulin is the only blood protein that appears in the colostrum, and it is the only protein fraction in which the new-born infant's blood is deficient. Evidently the colostrum is formed to provide the fetus with a supply of euglobulin for its blood, during the short period immediately after birth when proteins may be best absorbed without disintegration by digestive proteolysis. The importance of this lies in the fact that the protective antibodies of the blood are found associated with the euglobulin fraction, and that the quantity of protective antibodies found in the colostrum, the milk and the infant's blood varies directly with the euglobulin content of these fluids. Evidently the colostrum furnishes to the new-born mammal protective antibodies, which probably adds much to its capacity to resist infection in early life. If the infant does not receive colostrum it acquires euglobulin in its blood much more slowly, and is presumably in corresponding degree less resistant to infection. It is not probable that there is any equivalent substitute for human colostrum for new-born infants.

---

**Diagnostic Value of Determining Vital Capacity of Lungs of Children.**—WILSON and EDWARDS (*Jour. Am. Med. Assn.*, 1922, 78, 1107) adopted a simple method and technic for the determination of the vital capacity in children from six to sixteen years of age. A normal standard of 1.93 liters per square meter of surface area was established from a study of 362 children. A plus or minus 10 per cent deviation was allowed, thus giving a normal range of from 1.74 to 2.12 liters. The vital capacity may be read at sight from a chart in liters per square meter of surface area and in percentages of normal capacity. A normal standard of 15.5 cc for each centimeter in height was also indicated as another method of relating vital capacity measurement. An analysis of some of the factors expected to influence vital capacity measurements revealed that boys show a vital capacity 6 per cent greater than girls. The extremes of age gave values at the lower and the higher limits of the normal range established. The colored race showed a definitely lowered vital capacity. Poverty, environment and social status did not seem appreciably to influence the lung capacity. Activity and athletics tended to increase the vital capacity. Malnutrition and underweight for height did not lower the vital capacity. Overweight for height revealed an apparent reduction of vital capacity per square meter of surface area. Vital capacity measurement was a fairly constant measurement. A reduction of vital capacity measurement of 15 per cent or more from the average normal standard should be taken as an index for the need of further examination and study of the child to ascertain the cause of the falling below the standard.

## OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

**Pregnancy After Very Severe Disease of the Ovaries and Tubes.**—In the *Zentralblatt für Gynäkologie*, 1922, No. 4, p. 139, ARNOLD describes the case of a woman, aged twenty-seven, who was admitted to hospital with bilateral salpingitis and excessive inflammation about the uterus. She was treated conservatively and examined at intervals during the next five years. These examinations showed extensive inflammation of both tubes and ovaries. The uterus was anteflexed, hard, very little movable, and there was a very considerable exudate fixing the uterus in the pelvis. On one occasion incision was made in the posterior vault of the vagina and a free discharge of pus followed, which could be traced to the right side of the pelvis. The patient was then in hospital for three weeks. At these examinations the ovaries were found prolapsed, bound down by adhesions, enlarged and very tender on pressure. So great was the exudate that the tubes could not be distinctly made out. The patient next presented herself at the hospital in the sixth month of pregnancy and desired attendance at her home in labor. She gave spontaneous birth to a living child which suffered from ophthalmia. At the last examination the uterus was movable; the adnexa seemed to be free from adhesions, and there was a scar in the posterior vaginal vault where the incision had been made.

**Grape Sugar as a Stimulant to Labor Pains.**—MÜLLER (*Zentralblatt für Gynäkologie*, 1922, No. 4, p. 140) has used grape sugar in 40 to 50 per cent in concentration, given in doses of 10 cc intravenously after careful sterilization, to stimulate the pains of labor. In cases where there was no mechanical obstruction to delivery but the delay seemed to arise from lack of general strength on the part of the patient an excellent result followed without injury to mother or child. In 15 cases in which this method was tried a positive result followed in 9; some effect was produced in 3, and no effect in 3. The doses first given were 10 per cent concentration, but this was increased to 50 per cent and the effect produced by this solution lasted from thirty or forty minutes to one hour. The writer calls attention to various analyses of the blood during pregnancy, showing a lack of sugar in some cases. He examined 17 patients and found the blood-sugar diminished more than one-half in these cases. It is a curious and interesting fact that extracts of the ductless glands and toxins derived from various sources, when injected in pregnant women, will produce almost similar results. This seems to result from an irritation of the sympathetic nervous system, which produces contraction in the unstriated muscle in the intestine and uterus. The merit of the sugar solution consists in the fact that it is not a poison, is entirely consumed in the body and can do no injury.

**Cesarean Section.**—*The Journal of Obstetrics and Gynecology of the British Empire* devotes numbers 3 and 4, Volume 28, 1921, to the subject of Cesarean section. Thirteen papers are published in this number by the obstetricians of the British Empire of widest experience in Cesarean section. This number of the *Journal* is practically a monograph upon this subject. In addition, there are book reviews and abstracts of current literature, and a description of a collection of obstetrical instruments in the Museum of the Royal College of Surgeons of England.

Space does not permit us to quote at length from these interesting and valuable papers, but we may give a summary of the various opinions and methods studied.

MUNRO KERR writes the first paper upon the indications for Cesarean section. The weakness of the present operation is the fact that it leaves behind a uterus permanently injured and liable to rupture should another pregnancy occur. Were this objection done away with, the indications for the operation could be rightly extended. The writer believes that all deliveries should be carried out in hospitals or nursing homes, and were this done, one common objection to obstetric surgery would cease. He also states that it is impossible to make the practice of obstetrics too surgical, for, like other branches of surgery, its first essential is surgical cleanliness.

Contrasting Cesarean section with pubiotomy, he believes that the latter is especially suitable for contractions at the outlet of the pelvis. By his method of estimating the size of the head and pelvis, using principally the thumb, he is able accurately to judge of the comparative size of the child and the mother. Induction of labor does not come into competition with Cesarean section, in his mind. He urges a more thorough preparation of the vagina and cervix in all suspected cases before operation. He also would, if possible, after Cesarean section, deliver the placenta through the vagina, believing that by this procedure the risks of infection are lessened.

A fibroid tumor obstructing the passage of the child from the uterus justifies Cesarean section. In ovarian tumors complicating labor, Cesarean section is rarely necessary. The tumor should be removed and the child delivered through the vagina. Should it be impossible to dislodge the tumor, then a Cesarean operation should be done. In eclampsia the only cases in which Cesarean section is justified are those where pregnancy is well advanced with no dilatation of the cervix or attempted labor, and when after six hours there is no improvement from blood-letting, intravenous saline infusion and morphine. When eclampsia develops earlier than the thirty-second or thirty-third week, vaginal Cesarean section should be performed.

The writer believes that placenta previa is peculiarly suitable for Cesarean section, and that the operation may come to be the general method of treatment in all cases of the central and marginal varieties. In the lateral, rupture of the membranes and a slight separation of the lower pole of the placenta usually suffice. In primigravidae with central placenta previa, he believes that Cesarean section should always be practised.

In the majority of cases of accidental hemorrhage he would rely on quiet, warmth, morphine and pituitrin in doses of 1 cm. so soon as labor

pains begin. In his mind placenta previa far more often furnishes an indication for Cesarean section than does accidental hemorrhage. Where the uterus has been fixed before the pregnancy by some operation and conditions are such that vaginal delivery is impossible, Cesarean section must be done, and this is true with patients who have had the interposition operation. In elderly primigravidae with rigid cervix, the writer would perform Cesarean section if the umbilical cord had prolapsed, in the interest of mother and child. In impacted shoulder presentation, he believes the indication for Cesarean section rarely arises. Where the child is abnormal, if it is very large and a question of size and not of deformity or malformation, Cesarean section might be indicated. In future it is probable that cases complicated by a tense retraction or contraction ring may be treated by Cesarean section, and this is true of those patients where some extraordinary rigidity or contraction of the cervix or pelvic floor makes delivery through the vagina difficult and dangerous. It is obvious that cases may arise in which the condition of the mother, whose life is threatened by some serious constitutional disease, indicates that she should be treated by Cesarean section. In general, Kerr believes that twenty years hence the accepted indications for Cesarean section will be extended even beyond the limits suggested.

Kerr describes a method of performing the operation which he practises and in which he is greatly interested. He recognizes that the uterine scar after the classic operation is unsatisfactory. He believes that a better scar can be obtained by an incision through the lower segment. To obtain an ideal result with this method, infection must naturally be avoided. Unlike other operators he incises the lower uterine segment transversely. In closing the wound he stitches the lower end of the wound with catgut but the bulk of the muscle tissue is closed with linen thread or fine silk. He takes pains to suture the uterus while in a state of retraction as distinguished from that of contraction. He believes it possible by so doing to procure better approximation, and he would always deliver the placenta through the vagina if this can be done. Occasionally in his operations it is necessary to insert a blade of the forceps or both blades to deliver the child's head. At the time of writing his paper he had operated by this method 22 times. He makes a longitudinal incision, with the patient in the Trendelenburg position, reaching from below the umbilicus to the symphysis. After the abdomen is opened the bladder is dissected off the anterior uterine wall. The transverse incision is made in the lower uterine segment and a suture placed at each end of the wound to control any laceration at the ends, and after delivery to pull up the wound so that it can easily be stitched. By passing a hand behind the uterus the child is pressed out. Sometimes one blade of the forceps is used to force out the head, very rarely both blades. When the child has been extracted and the cord tied the cord is dropped through the cervix, so that it may be a guide to the delivery of the placenta. The wound is pulled up by the two lateral stitches and the mucous membrane closed by catgut, the muscle by linen thread and a third layer of catgut to replace the bladder. A large retractor in the lower part of the abdominal wound gives easy access to the lower segment. He believes that this incision cuts through a less vascular area than the higher one; that the bleeding is extraordi-



narly slight unless the wound opens the vessels at the side; the wound is thin and easily closed. A further great advantage is the fact that the wound in this area is at rest during the early days of the puerperal period, and because the lower uterine segment does not become fully stretched until labor is well advanced, the scar is in a safer region than in the ordinary longitudinal incision. In 22 cases he has had one fatality; there has been one spontaneous delivery after the operation and on 4 cases a second Cesarean section has been done. In 2 of these cases the scar was very carefully examined and no trace was found of the former wound. In 1 of his operations the patient was at term without labor. The wall of the uterus was much thicker and the lower segment more difficult to reach. In 1 case the amniotic liquid had escaped, and the head of the child lay transversely at the pelvic outlet. After making the incision the operator could not raise the head out of the pelvis. The incision was extended longitudinally and the child was delivered.

---

**The Relationship Between Toxemia of Pregnancy and Uterine Sepsis.**—KELLOGG (*Amer. Jour. Obst. and Gynec.*, April, 1922, p. 366) has studied 400 toxemic cases to observe the relationship between toxemia and sepsis. He believes that symptoms of toxemia call for treatment so soon as discovered, and that eclampsia is never a self-limited disease. The mortality of toxemia with convulsions in hospital practice he places at 25 per cent, of whom 90 per cent died within thirty-six hours. The mortality in hospital practice of toxemia without convulsions is 2.5 per cent, a very considerable death rate. Of those toxic patients who survive convulsions, 9 per cent die of uterine sepsis. In toxemics who have no convulsions, uterine sepsis causes death in 0.5 per cent. Of unselected non-toxemic cases 2.5 per cent became septic; 14 per cent of toxemics without convulsions became septic; 25 per cent of toxemics with convulsions became septic irrespective of the method of delivery. Toxemic patients are four times as likely to become septic under similar methods of delivery as unselected and non-toxemic patients. Convulsions increase the liability to sepsis; the absence of convulsions slightly diminishes it. These patients are more likely to have difficult operative deliveries with a higher septic rate. These facts indicate that in delivering toxemic patients we should avoid, if possible, capital operations. The writer would induce labor by bags, unless he could start labor with catharsis. The patient should be allowed to deliver herself if possible, or be delivered by the application of forceps. Morphine and blood-letting should be employed as indicated. He adds a word of caution concerning the action of bags, that when the bag fails to dilate the cervix and bring on labor, it should be promptly removed and delivery completed by manual dilatation, vaginal or abdominal section. The writer states that symptoms of toxemia of pregnancy call for quick action and good judgment.

---

**Rupture of the Scar of a Previous Cesarean Section.**—GOUGH (*Lancet*, March 11, 1922, p. 485) describes the case of a patient who had a Cesarean operation two years before her last admission to hospital. At the previous operation the uterine wall was closed with two layers of catgut. The patient came to hospital at full time, complaining of

pain in the back and lower abdomen. She was well enough to walk, but within four hours after admission she became very ill with symptoms pointing to some intra-abdominal complication, and the abdomen was opened. A quantity of blood-stained fluid was found, and in the left broad ligament and under the utero-vesical peritoneum there was a collection of blood. It was found that this was due to the giving away of the uterine scar at its lower end. The wall of the uterus was incised at one side of the rupture and a dead child extracted. The old scar was then removed and the uterine wall closed with catgut. The patient made an uninterrupted recovery.

---

## GYNECOLOGY

---

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA  
AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY  
OF PENNSYLVANIA, PHILADELPHIA.

---

**Ovarian Autotransplantation.**—As a result of his experience with the transplantation of ovaries in the course of gynecological surgery, GIRARD (*Calif. State Jour. Med.*, 1922, 20, 21) concludes that autografting of ovaries is a perfectly safe and rational procedure and is indicated, except in cases of malignancy or ovaries grossly infected, in all patients requiring removal of the ovaries, with or without hysterectomy. Ovaries which require removal, in his opinion, are; (a) Badly traumatized ovaries with much raw surface on the capsule; (b) ovaries showing considerable cystic degeneration, and (c) ovaries having an impaired blood supply. Cystic degeneration of ovaries is no barrier to autotransplantation and ovaries removed in conditions of pyosalpinx can be transplanted, provided the ovaries themselves are not grossly infected. He believes that autotransplantation lessens and delays ablation symptoms following castration and in some cases affords complete freedom from symptoms of artificial menopause. That the autografts functionate is shown by periodic increase in size and tenderness of the grafts with amelioration of the ablation symptoms and, when the uterus remains, by menstruation. Reasonably healthy and undamaged ovaries should be left in situ with or without the uterus and autotransplantations should be used to carry on the physiological functions of the ovary only in those cases where, for reasons given above, both ovaries must be removed. The technic of autografting is simple and adds no extra risk to the operation. In all cases the ovaries are completely removed and the uterine end of the tube is resected by a V-shaped incision into the cornu of the uterus. The ovaries are wrapped in a gauze sponge and placed in normal salt solution of body tempera-

ture. After the peritoneal toilet has been completed a pocket is made by blunt dissection between the peritoneum and the under surface of the rectus muscle, on either one or both sides of the incision, according to the number of grafts to be used. The ovaries are then carefully inspected and areas of cystic degeneration are culled out after which the remainder is cut into disks  $2 \times 2 \times \frac{1}{2}$  cm. and from one to three of these disks transplanted into the already prepared pockets. No sutures are used to hold the grafts in place. The abdominal wall is then closed in the usual manner.

---

#### **Radiation Versus Surgery in the Treatment of Uterine Cancer.—**

The working rules that have been adopted by CROSSEN (*Jour. Missouri State Med. Assn.*, 1922, 19, 55) are that in the advanced inoperable cases as well as in the borderline cases of uterine cancer, radium is our most effective remedy. The palliative effect is nothing short of wonderful. The enlarged carcinomatous cervix with its bleeding papillary masses melts away as if by magic and the cavity closes, largely or entirely by granulation. But it should be remembered that radium is two-edged and may do as much harm by causing excessive scar tissue contraction or actual stimulation of the cancer cells as it may do good, consequently its use requires decided caution. It is hoped that in time the curative effects of radium may be extended to the limits of the pelvis, but that ideal has not yet been attained. In some extensive cases the cancer is completely eliminated by the radium; this result is attained, however, in only a small proportion of the cases. It may be hoped for but it is so infrequent in the classes of cases under consideration that the remedy must be presented to the patient as essentially a palliative measure, with only a possibility of cure. It is advisable to employ also deep roentgen-ray therapy to affect the cancer cells lying beyond the effective reach of the radium, but even this combination must be classed generally as palliative rather than curative. In clearly operable cases, that is, in those early cases apparently still confined to the uterus, Crossen feels that immediate removal of the uterus and adjacent tissue likely to be involved is the safest plan. Theoretically we should be able to cure these patients with radium with as great certainty and with far less danger than with the knife; but so far the actual results in cancer of the uterus do not justify displacement of the knife by radium in these early cases. In something over one thousand collected cases of carcinoma of the cervix treated by radium five years previous to the reports, about 20 per cent were cured—approximately the same percentage as by radical operation. When the cases were divided into classes it was found that more of the advanced and borderline cases were cured by radium than by operation, while of the early operable cases the percentage of cures by radium (31 per cent) fell decidedly below that by operation (40 to 45 per cent). We know what can be done with the knife in the individual case but we do not know the extent of the effectiveness of radium in an individual case until it is tried in that case and in the time required for trial by radium the chance of cure by operation slips away. In order to give the patient the best chance of cure in these early cases, it is advisable to employ both radium and operation. First give a heavy dose of radium, the same as though depending on it to effect a cure, then within a week or ten days do the

radical operation. The operation should be carried out within a short time after the radium treatment because later the radium treatment may have caused such marked connective tissue changes as to increase very decidedly the difficulties and hazard of the operation. This plan of treatment for the early case is based on the assumption that the patient is a good operative risk. If the patient has some serious complication making her a poor operative risk, then her best chance of survival cancer-free may be through radium without operation. The decision for or against operation and of the extent of operation, turns on a balancing of the hazards pro and con—the hazard of operation, the chance of failure of radium to kill the cancer cells in that individual, and the chance of metastasis near and far. On account of the latter danger, it is advisable to supplement the other treatment by deep roentgen-ray treatment.

---

**Urethral Stricture in Women.**—Stricture of the urethra in women is a condition which is very often overlooked, according to STEVENS (*Cal. State Jour. Med.*, 1922, 20, 51) although it may be responsible for marked functional and organic disturbances in the genito-urinary tract in this sex. It is a generally accepted idea that strictures of the female urethra are very uncommon. While this is true so far as the lumen of the canal is concerned, strictures at the meatus on the other hand are frequently encountered. As the female bladder is especially sensitive to reflex influences, marked subjective symptoms are often produced by comparatively slight obstructions. It must be remembered however, that these symptoms may be partly due to the accompanying urethritis or trigonitis. Frequent urination is the most common symptom of which these patients complain. The next most common symptom is pain which is referred to the urethral or bladder regions. The diagnosis is best made by means of the olive-tipped bougie. The majority of these strictures should be treated by means of gradual dilatation, absorption of the constricting exudate being best promoted by this procedure. In the presence of scar tissue however, meatotomy, internal urethrotomy, or external urethrotomy with resection of the scar tissue is often indicated. The symptoms improve, as a rule after two and disappear after five dilatations, recurrence being very unusual if treatment is not too abruptly discontinued.

This subject has also been carefully presented by WYNNE (*Surg. Gynec. and Obst.*, 1922, 34, 208), who states that the great majority of strictures are single, although multiple ones have been reported; and although the stricture may be located in any part of the urethra, the external meatus and anterior portion are the favorite sites. He classifies strictures as traumatic, inflammatory, neoplastic, congenital, senile and unknown, which terms are self-explanatory. The onset is usually gradual and the course progressive. In some cases the only symptoms noted by the patient are the small stream voided and the length of time required for the act of voiding, but in the great majority of cases there is also some degree of dysuria. The diagnosis is made by examination with sounds or, preferably, olive-tipped or bulbed bougies as advised above by Stevens. In certain cases the strictured area can be felt through the vagina. The endoscope is necessary for a complete examination. Wynne treats these patients by gradual dilatation of the

stricture with sounds, bougies, or Hegar dilators over a considerable period of time. This operation is carried out after a local anesthetic has been applied to the urethral mucous membrane. The dilating instruments should be generously lubricated before insertion and the largest instrument passed at any sitting should be left in place for from ten to fifteen minutes. The size of the dilators used must be determined each time by the degree of pain caused. It is necessary to avoid any severe pain when the treatments are so frequently repeated, as well as to avoid considerable trauma. At first daily treatments are given, but later the intervals between sittings can be increased, and the treatments should be continued over a period of several months. These patients ought to be warned that recurrences are common, and that for this reason they are to return several times a year for dilatation.

---

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

---

**On the Claim that Some Typhoid-Paratyphoid Strains Survive the Milk Pasteurization.**—KRUMWIEDE and NOBLE (*Jour. Infect. Dis.*, 1921, 29, 310) found that "there is no evidence that bacilli of the typhoid and paratyphoid group even in small numbers, will survive heating to 60° C., for twenty minutes," suggesting that the apparent heat resistance of the strains reported by TWISS (*Jour. Infect. Dis.*, 1920, 26, 165) was due to the test method employed, namely, the use of cotton plugged flasks submerged to twice the depths of the milk. The authors used 27 typhoid cultures recently isolated from carriers, 7 paratyphoid A, 12 paratyphoid B and 4 enteritidis cultures. Milk was sterilized and 100 cc of it was infected with the cultural growth from two twenty-four hour agar slants suspended in salt solution. The bacterial suspension was added after the milk had reached 60° C., rubber stoppers were inserted, the bottles vigorously shaken and completely submerged in a water bath for fifteen minutes. No bacteria survived a pasteurization period thus limited closely to fifteen minutes at 60° C.

**Antirabic Vaccination by Means of Desiccated Virus.**—With slight modifications, D'AUNOY (*Jour. Infect. Dis.*, 1921, 29, 261) has employed a desiccated virus prepared according to Harris on account of its capability of production in a short time and preservation over indefinite periods. Full grown, healthy rabbits, averaging 2200 gm. were inoculated into the lateral ventricles after trephining with about 0.004 mg.

of desiccated fixed virus in 1 cc of sterile salt solution. The animal developed symptoms in six or seven days and when complete paresis had intervened, was killed by ether narcosis. The cord and brain were then removed aseptically, and the membranes were stripped off by needles. By grinding with salt solution, the nerve tissue was brought to a coarse paste in a mortar. Carbon dioxide snow was then added with constant mixing and triturating until the mass had solidified. The mass was then placed in a meat grinder and kept at a temperature of about 12° C. for a few hours, a small amount of CO<sub>2</sub> again added and quick grinding accomplished. The ground material was spread in a thin layer and dried in a Scheibler desiccator at from 12 to 18° C. With a vacuum of 2 mm of mercury, and phosphoric anhydride, complete desiccation was procured in about thirty-six hours. The dried virus was kept in large glass tubes in a dark place at from 10 to 15° C. Control cultures of every batch of virus were instituted. The unit or "minimal infective dose" consists of the least amount of virus which within five days after preparation will cause paresis in a 2400 gm. rabbit on the seventh day following intracerebral injection. A virus containing 300 to 500 "minimal infective doses" per mg. was readily produced. It will lose no infectivity at 10° C. for over two years and will last about three years at 8 to 12° C. Adults were given 11 treatments of a total of 17,750 "minimal infective doses" except in severe head injuries when 15 treatments of a total of 25,750 m. i. d. were administered subcutaneously. Only 1 death following complete treatment is reported in 1538 treated patients; 697 injuries by animals proved to be rabid. No paralysis or other untoward effects were encountered in the treated persons. The author feels that his results "on the basis of comparison with similar reports on the use of the original Pasteur dried cord method, argue for the efficaciousness and safety of the desiccated virus method of prophylactic antirabic vaccination."

---

**Botulism from Cheese.**—Evidence that botulism is widely disseminated in this country can be found in the sporadic reports which have appeared in recent years. Although it was once thought that the botulinus toxin was produced only in the presence of meat protein, Diekson was able to find it in the presence of vegetable protein and now NEVIN (*Jour. Inf. Dis.*, 1921, 27, 226) reports the recovery of both *B. botulinus* and its toxin from home-made cottage cheese, after the ingestion of which three persons died. Two cases presented paralysis of the muscles of deglutition, suffusion of the face, ptosis, total dilatation and failure of the pupils to react to light and paralysis of the muscles of the throat with difficulty of speech. The third patient was unable to swallow. There was no loss of consciousness or paresis of any other part of the body. Subcutaneous inoculation of 3 cc of an emulsion of the cheese, after forty-eight hours' incubation at 37° C., killed guinea-pigs within thirty-six hours. By anaërobic methods, a Gram-positive, motile, oval, sporebearing bacillus was isolated. No capsule could be demonstrated, gelatin was liquefied slowly and milk coagulated in three days. Many carbohydrates were fermented with the production of gas and the odor of butyric acid. A potent toxin was produced on a peptone-free medium. Guinea-pigs

were killed in four days with 0.0005 cc of the filtrate of a seventy-two hour culture. A protective serum was produced in rabbits against the homologous toxin. The author states that this is the first time that *B. botulinus* has been isolated from cheese, that a soluble bacterial toxin has been detected in cheese and that *B. botulinus* has been isolated in America.

---

**Studies on the Chemotherapy of the Experimental Typhoid Carrier Condition.**—Appreciating the menace of typhoid carriers to society and conceiving the probability that certain anilin derivatives may be toxic to the typhoid bacillus in vivo, BECKWITH (*Jour. Infect. Dis.*, 1921, 29, 495) administered auramine, acriflavin, proflavine, pyronine G and new fast-green 3 B—all of which showed bactericidal action in bile and serum—intravenously into rabbits in which the typhoid carrier state had been produced by the Gay-Claypole technic. It was found that acriflavine and proflavine were more germicidal in the presence of serum than in its absence, while bile usually depressed the activity of the stains as much as serum. All the stains save new fast-green 3 B, although bactericidal to *B. typhosus* in vitro, did not sterilize the gall-bladders when introduced intravenously. Auramine was too toxic and the others were excreted through the urine rather than the bile. The writer believes that new fast-green 3 B “offers possibilities as a germicide in vivo for *B. typhosus* in gall-bladders of experimental rabbit carriers,” inasmuch as it retains its activity in serum and bile and is excreted through the bile when administered intravenously, although it does not clear up the condition in all animals. The dye changes readily from the sol to the gel state and may be very toxic to the animal.

---

**Comparison of Formol and Wassermann Reactions in Diagnosis of Syphilis.**—Following the report of Gaté and Papacostas, that pooled syphilitic serum was coagulated by a small quantity of formalin, while nonsyphilitic serum failed to give the reaction, ECKER (*Jour. Infect. Dis.*, 1921, 29, 359) conducted 500 comparative tests, employing the ice-box method for the Wassermann reaction with syphilitic fetal liver, normal human and beef-heart antigens. The technic of “formol” method consisted in adding two drops of Schering’s or C. P. formalin, in both acid and neutralized solution, to 1 cc of clear serum, shaking gently in tubes plugged with cotton or more tightly and incubating for from twenty-four to forty-eight hours at temperatures of either ice-box, room or 37° C. Whereas, in a series of 400 comparative tests Gaté and Papacostas found agreement in 85 per cent, only 37.09 per cent of the total number of positive reactions agreed in the writer’s series, which compared more closely with the 27.27 per cent as found in a similar work by Pautot. Forty-four per cent of the formol positives were of the + type, and of these, 13 were positive by the Wassermann. The writer concludes that “the reaction as it stands is of no diagnostic value because of its failure to react in clinically and serologically clear-cut cases of syphilis and the occurrence of positive reaction in the absence of the disease.”

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

**Tuberculosis of Husband and Wife.**—BARNES (*Am. Rev. Tuberc.*, 1921, 5, 670) states that the histories of 229 consecutive widowed patients admitted to the Rhode Island State Sanatorium, 1905 to 1921, show that 93, or 40 per cent, lost their consorts by death from tuberculosis, a tuberculosis mortality over three times that of the married people of the community. Immunity from many diseases is short-lived and until much more convincing evidence of permanent immunity against tuberculosis conferred by childhood infections is forthcoming, a cautious logic will not accept the confident statements that are being made as to the impossibility or rarity of adult infection.

**The Etiology of Typhus Fever.**—The past twelve years have witnessed an energetic investigation into the precise nature of the virus of typhus fever. A number of bacteria have been brought forward as causal agents of the disease. Two of these attracted special attention; namely, *Rickettsia prowazekii* of da Rocha-Lima and *B. typhi exanthematici* of Plotz. Several years ago, OLITSKY (*Jour. Infect. Dis.*, 1916, 19, 811) was led to accept the etiological relationship of Plotz's bacillus to typhus fever by the fact that he found specific antibodies against the organism in the blood of typhus patients; that with it, it was believed, experimental typhus in guinea-pigs had been induced and that a similar bacterium was recovered from typhus-infected lice. Olitsky (*Jour. Exp. Med.*, 1921, 34, 525) revises his judgment concerning Plotz's bacillus, for he finds that in the early stages of typhus fever in guinea-pigs the typhus virus can be obtained wholly free from admixture with any of the ordinary bacteria. Furthermore, the body of the guinea-pig reacting to the virus of typhus fever is readily invaded by a variety of bacteria whose presence complicates the typhus infection, but which have no etiological relation to the specific disease, typhus fever. Olitsky showed that during the period of incubation and before the onset of fever no ordinary bacteria appear in the cultures, while on the first day of the febrile reaction different bacteria were found in 6 of 26 guinea-pigs cultured; on the second day, in 10 of 16; on the third day, in 3 of 4; and on the fourth day in cultures of all of the 4 guinea-pigs observed. The findings indicate that the virus of typhus fever is distinct from ordinary cultivable bacteria, and, as the disease set up by the virus progresses, the infected guinea-pigs become subject to



invasion by secondary or concurrent bacteria which thus induce a mixed infection. The bacteria which under the influence of the virus of typhus fever thus invade the body of the guinea-pig are of several kinds, and vary not only among themselves, but also with the day of the fever on which the examination is made. Thus, on the first day of the fever, Plotz's bacilli were recovered twice and anaërobic streptococci, *proteus* bacilli, aërobic diphtheroids, Gaertner type bacilli, and *Staphylococcus aureus*, each once. On the second day Plotz's bacilli were found four times, anaërobic streptococci three times, Gaertner type bacilli, aërobic diphtheroids, *Bacillus welchii*, aërobic Gram-positive diplobacilli, and *Staphylococcus aureus*, each once. On the third day Plotz's bacilli were recovered once, as were anaërobic streptococci and Gaertner type bacilli. On the fourth day, *Staphylococcus aureus* was found twice and Plotz's bacilli and *Bacillus proteus* each once. The variation in the kind of bacteria, as well as the lack of predominance of one kind over another during the different stages of the febrile reaction in guinea-pigs, led Olitsky to infer that they occur concurrently with the typhus virus. And since the more unusual of these organisms, the Plotz bacillus, the anaërobic streptococcus, the aërobic diphtheroid, and the diplobacillus are non-pathogenic for guinea-pigs, while the more common bacteria such as the Gaertner type bacillus, Welch's bacillus, the proteus bacillus, and the staphylococci induce distinctive effects, and since all the bacteria could be suppressed without their reappearance in guinea-pig passages of the virus containing them, Olitsky believes that they are independent and unrelated to the true virus of typhus fever.

**Viability of the Colon-typhoid Group in Carbonated Water and Carbonated Beverages.**—KOSER and SKINNER (*Jour. Bact.*, 1922, 1, 111) found that under the conditions of their experiments carbonation exerted a distinctly harmful effect upon the members of the colon-typhoid group and that their period of viability in carbonated water was much shorter than in plain tap water. The destructive effect of the CO<sub>2</sub> was especially marked at room temperature, 19° to 23° C., and less so at 10° C. The authors state that in a "non-acid" beverage, the organisms may persist for a slightly longer period than in carbonated water. In beverages containing 0.094 per cent or greater amounts of citric or lactic acids, the death-rate is very rapid and is apparently due to the effect of these acids, irrespective of the CO<sub>2</sub>. *B. Typhosus* and *B. paratyphosus* B are more readily destroyed by CO<sub>2</sub> than is *B. coli*. The spore forms of a common aërobic, *B. mesentericus*, and of a common anaërobe, *C. sporogenes*, were found to be quite resistant to carbonation, surviving one month at room temperature with no apparent diminution in numbers. The authors emphasize the fact that throughout their experiments the water used for carbonation and for preparation of the various beverages was an ordinary city supply of low mineral content. They state that under certain conditions, as for example in carbonated water of high mineral content, it is possible that non-sporeforming organisms may remain alive for longer periods than those reported. This possible influence of certain inorganic salts upon the viability of microorganisms in a carbonated environment has not been studied in the present investigation. The authors state

emphatically that the results obtained in the investigation do not warrant the conclusion that water of a low sanitary quality can be used by the industry in the preparation of carbonated beverages, or that carbonation can be relied upon to destroy evidence of pollution. They state that in many instances, particularly during the summer months, beverages are consumed within a few hours after their preparation and it is obvious that under these conditions pathogenic organisms, if originally present in the water, may survive carbonation and reach the consumer.

---

**Table Utensils as Sources of Tuberculous Infection.**—FLOYD and FROTHINGHAM (*Am. Rev. Tuberc.*, 1922, 6, 51) state that the table utensils used by open consumptives may occasionally harbor virulent tubercle bacilli, even after more careful washing than is customary in the average home. The water used to wash such utensils quite frequently contains virulent tubercle bacilli. Floyd and Frothingham conclude from their experiments that it seems evident that the table utensils used by an open consumptive may be not only a menace to the patient himself and to others in his family, but also a general menace when the patient eats in public places. They state that the inference also seems warranted that the dish towel used to wipe these utensils must become contaminated with virulent tubercle bacilli, and the more frequently it is used the more bacilli accumulate, so that if employed for several days without thorough washing, a common practice in many homes, it becomes more and more a depository of tubercle on the just washed utensils. It would seem, therefore, that the only way to control the danger of spreading tuberculosis by such utensils is to thoroughly sterilize the patients' tableware and the dish towel employed to wipe it after each meal, and the simplest method to accomplish this is to boil them for several minutes.

---

**The Present-day Sources of Common Salt in Relation to Health and Especially to Iodine Scarcity and Goiter.**—HAYHURST (*Jour. Am. Med. Ass.*, 1922, 78, 18) states that while iodine may occur in natural deposits along with chlorine, usually in the form of the sodium salt, it is never obtained from such sources commercially because it occurs in too limited quantities. Chili saltpeter is the chief source of iodine. The sea is the great storehouse of iodine where it completes a cycle from inorganic compounds to organic life and return. The salts of sea water are constant in both quality and quantity. Sodium chloride comprises 77.8 per cent, magnesium chloride 10.9 per cent with many other compounds, including sodium iodide, composing the remaining 11.3 per cent. It has an average total salinity of 3.4404 per cent. All of the salts in sea water are unusually soluble in plain water. The great solubility of sodium iodide accounts for its almost complete absence from the land surface and, perhaps, for some of the peculiarities noted in regard to the incidence of goiter. Authorities are agreed that goiter is infrequent in both animals and man along the sea. The same is true also of some fish (salmons) which inhabit both fresh water and sea water, tending to develop goiters in the former, and none in the latter. Apparently sea animals do not have goiter. Practically all salt used in the United States for dietary consumption is obtained from inland sources by the

evaporation of brines, which for the most part are inherently free of iodine. Irrespective of the source, whether sea water or inland deposits, the modern processes of preparing and purifying salt free it from all traces of iodine, as well as its other naturally associated elements, many of which are identical with the body fluids of higher animals. Hayhurst concludes that an analogy should be drawn from sea life and a precept taken from evolution. Of the dependable source of iodine in Nature—sea air, sea food and sea water—it is to sea water, used perhaps in place of common salt as a condiment, that inland dwellers should look. This substitution would appear to offer a complete solution to the iodine deficiency problem, if nothing else; while evidence would tend to show that other constituents of sea water have also an undoubted place in the economy of the higher animal organism, perhaps to the extent of precluding some diseases which are likewise possibly of a deficiency type. Common salt for dietary purposes should include not only sodium chloride but also sodium iodide, and undoubtedly many of its other original concomitants. For geochemical reasons, great care should be taken in selecting its source, if it is not actually derived always from sea water. It must then be handled commercially in a manner to retain these constituents.

---

**The Destruction of Tubercle Bacilli in Sewage by Chlorine.**—CONROY, CONROY and LAIRD (*Am. Rev. Tuberc.*, 1922, 6, 63) state that sewage from a tuberculosis sanatorium nearly always contains living tubercle bacilli. The use of a chlorine machine is a practical means of ridding such sewage of tubercle bacilli. Two machines should be used to insure continuous disinfection. Preliminary treatment of the sewage is necessary to reduce it to a liquid form, and to prevent the floating of solid particles containing tubercle bacilli in water courses.

---

**Adequate Industrial Medical Service for the Small Plant.**—McCord and MINSTER (*Jour. Indust. Hyg.*, 1922, 3, 363) state that the number of workers employed in small factories exceeds the number engaged in work in plants of 500 or more employees. Proportionately, work conditions are less satisfactory in small factories than in larger plants. It is desirable that some means be found to apply to the small plant the same type of health conservation measures that have proved so successful and so valuable in larger plants. The experience of a group of industrial health workers in a small plant averaging one hundred and fifteen employees is recorded. The results of such work have been of sufficient benefit to justify the assertion that this procedure may successfully be applied to small plants in general.

---

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only with the distinct understanding that they are contributed exclusively to this JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

Dr. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

AUGUST, 1922

---

ORIGINAL ARTICLES.

THE ACTION OF DIGITALIS IN CASE OF AURICULAR  
FIBRILLATION AND FLUTTER.\*

THIRD LECTURE

BY THOMAS LEWIS,

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND.

THE original observations upon which this lecture is largely based have been carried out by my collaborators and myself during the past twelve months to determine if the reaction of auricular fibrillation and auricular flutter to therapeutic doses of digitalis may be explained by the theory that these two disorders of heart rhythm are essentially due to circus movement.† First we will consider the action of digitalis upon the rate of the ventricle, and later we will consider the main problem of its action on the auricle. As will appear, knowledge of the first is relevant when we explore the second problem.

**The Nature of Digitalis Block.** The question as to how digitalis produces heart-block, the universally recognized cause of ventricular slowing in cases of auricular fibrillation, is one upon which a conflict of opinion exists. The evidence is not of so simple a character as it was once thought to be. The discussion is rendered

\* Based on observations carried out on behalf of the British Medical Research Council. The Nathan Lewis Hatfield Lecture, delivered before the College of Physicians of Philadelphia, May 5, 1922.

† Especially associated with me in the most recent observations have been Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Iliescu, of Bucharest; we have also received much assistance from Dr. A. N. Drury, who has for some years worked actively upon closely allied problems.

of more consequence because precisely similar problems arise in the case of ventricular slowings other than those due to digitalis and in other forms of slow ventricular action. The argument turns, as we shall presently see, mainly upon the reaction of the ventricle to atropine.

We start with the simple and uncontested fact that digitalis produces ventricular slowing in cases of auricular fibrillation; and we conclude from evidence in our possession that this retardation is due to block at the *A-V* junction.<sup>8</sup> Experiment teaches us that *A-V* block may be produced by digitalis in one of two ways, by increasing the tone of the vagus (an indirect effect exerted upon the junctional tissues) or by a direct action on the junctional muscle.<sup>3, 11, 16</sup> The action, whether direct or indirect is exerted, according with the indications of recent experiment, upon that portion of the junctional tissues termed the *A-V* node.<sup>11</sup> The direct and indirect action each has the same end-effect; each produces a condition at the *A-V* node rendering it less capable of conveying impulses. The immediate effects upon the tissue are not quite the same; in the case of the nerve effect, we have to deal apparently with a reduced rate of recovery of the tissue; in the case of the direct action we have to deal apparently with a prolongation of systole, whereby the time allowed for subsequent recovery is reduced. Be that as it may the end-effects are both declared as lesser or greater degrees of block. Block at the *A-V* junction is the only known means by which digitalis can influence the rate at which the ventricle will respond to an auricle in a constant and unaltered state of fibrillation. Is this block produced by a direct action or by an indirect action through the vagus in clinical fibrillation? The problem would appear easy to solve. Digitalis slowing is produced in a case of fibrillation and the patient is then atropinized. The atropine paralyzes the vagus and the ventricular rate returns to about its former level. What more natural than to conclude that digitalis exerts its action through the vagus. That is the conclusion to which Maekenzie came,<sup>12</sup> when he first used atropine for this purpose. But, as Cushny<sup>1</sup> has very properly pointed out, the problem does not end here. Cushny's argument is one of some intricacy and has not been understood widely and clearly. It may be illustrated diagrammatically (Fig. 1). Let us suppose that the line *cc* represents the level at which the ventricle beats in response to a fibrillating auricle when the patient is uninfluenced by drugs; and let us further suppose that this rate is reduced from *c* to *e* under the influence of digitalis given in therapeutic doses. Atropine is now given, and the rate returns, let us say, from *e* to *c*. The fall which digitalis produced is completely wiped out by the action of the atropine. Yet we are not justified in concluding that the digitalis fall of rate from *c* to *e* is vagal in origin. As Cushny has shown, if an

initial dose of atropine is given in the predigitalis stage, the rate is lifted temporarily to *a*. In other words, the original level *c* was maintained at a comparatively low point by normal reflex vagal tone; and when this level is further reduced (to *c*) by digitalis, the subsequent rise produced by atropine may be attributed to one of two effects: (1) To the abolition of the original reflex vagal tone prevailing at level *c* and still maintained after digitalization, or (2) to the abolition of a digitalis vagal tone.

To obtain *proof* that the fall on digitalis is due entirely to an increase of preëxisting vagal tone, one view which has been held of the action of digitalis, it would be necessary to show that atropine can raise the rate of the digitalized heart from level *c* to level *a*; for atropine, given in a sufficient dose to completely paralyze the

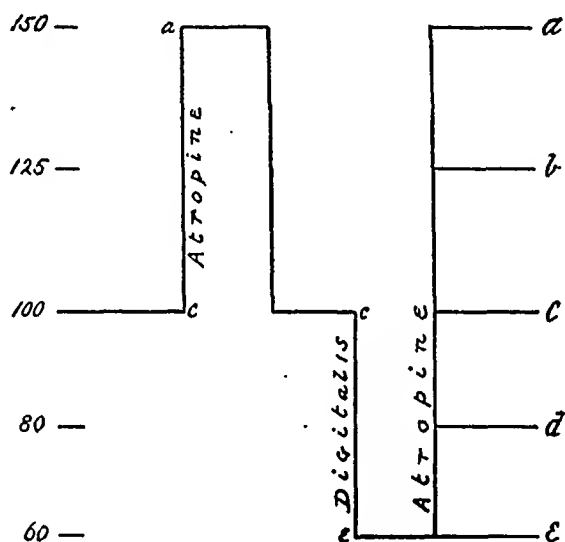


FIG. 1.—A diagram of the reaction of the ventricle, in auricular fibrillation, to digitalis and atropine. The diagram illustrates the text description.

vagus, should abolish, not only the original reflex vagal tone, but also that portion of the final vagal tone which has been superadded by the digitalis. The view may be held justifiably that the rise from *e* to *c* under atropine, is due, as was the original rise from *c* to *a*, to the abolition of normal reflex vagal tone and that the fall from *c* to *c* under digitalis was in reality the effect of a direct action which has been uninfluenced by the second dose of atropine. The level (*e*) at which the ventricular rate stands after digitalis and atropine is far below the level (*a*) at which it stands under atropine alone, and this should not be the case, providing that the digitalis fall is purely vagal, and if a dose adequate to abolish all vagal action is given on each occasion. Thus, it is evident that the final rise under atropine from *e* to *c* cannot be used as proof that the action of digitalis is vagal.

On the other hand it cannot be used as proof that the action is purely a direct one, the second view of digitalis action which has been held. *Proof* of a purely direct action would be obtained only if the second and adequate dose of atropine failed to produce a rise, namely, if the level remained stationary at  $e$ . It may be argued that since the rise from  $e$  to  $c$  is no greater than the rise from  $c$  to  $a$ , this relation constitutes evidence that both these rises are due simply to the abolition of the original reflex vagal tone, and that digitalis vagal tone plays no part in the fall  $c$  to  $e$ . This argument is only valid if a certain measure of vagal tone produces equal falls of ventricular rate from different initial levels and if we can be sure that when the ventricle slows under digitalis *the original measure of reflex vagal tone is maintained*; but the first assumption is scarcely justified, since a halving of ventricular rate is produced more easily when the rate of the ventricle is initially high than when it is low, and a halving of rate at a high level means a much larger fall in the number of beats per minute than does halving at a lower rate. In respect of the second assumption it may be argued that, when the heart slows under digitalis, the natural reflex vagal tone would tend to pass into abeyance and might vanish entirely.

We are left therefore in this position. Proof of uncomplicated vagal action requires a lift of rate from  $e$  to  $a$ . Proof of uncomplicated direct action requires maintenance of the level at  $e$ .

Now, neither one nor the other form of curve characterizes the actual reaction. The rate does rise when an adequate dose of atropine is given, but it rises to very different levels in different patients. In the series described by Mackenzie and by Cushny, the rise was generally either to a level intermediate between  $e$  and  $c$  or actually, as in Mackenzie's case, to  $c$ . It will be clear that the less the rise, the more is a direct action evidenced; the greater the rise, the more is vagal action evidenced; but that, so long as there is a rise, but a rise which fails to reach level  $a$ , *proof* of an uncomplicated action, direct or indirect, is not forthcoming.

**The Dose of Atropine.** The assumption that the dose of atropine given is adequate completely to paralyze the vagus is one of such consequence to the argument that it needs to be explored in some detail.

Actually the dose required to paralyze the human vagus has not been ascertained either for normal subjects or for cases of fibrillation, digitalized or undigitalized. The general assumption appears to be that one-fiftieth of a grain of the sulphate given hypodermically is sufficient.

This assumption appears to be based in part upon the belief that atropine has an "all or nothing" action; that if the ventricle is released at all, it is fully released. The last belief is not well founded. If atropine is injected intravenously repeatedly and in minute doses into dogs, it is not difficult to show that the drug first abolishes

the effects of weak vagal stimulation, and that further doses are required before the effect of strong vagal stimulation disappears. In dogs weighing 10 kgs. a dose of 0.2 to 0.4 mg. of atropine will abolish the effects of weak stimulation; in the same dogs doses of 0.4 to 1.0 mg. are required to abolish the effects of strong stimulation. The dose required to produce complete paralysis is approximately 0.05 to 0.1 mg. of atropine per kilo body weight. Calculated on the same bases for a human subject of 75 kilo weight, the dose required would be 3.7 to 7.5 mg. (or approximately one-seventeenth to one-ninth of a grain). From this calculation it might be anticipated that one-fiftieth of a grain given to the human subject would on direct tests prove to be inadequate. At the same time it should be noted that while in dogs doses of from 0.2 to 0.4 mg. will not abolish all reaction, yet they very notably reduce the reaction to strong stimulation of the nerve. Thus, it is to be inferred that since one-fiftieth of a grain given to a patient is sufficient to produce a conspicuous rise of ventricular rate, a large subsequent rise of rate on completely saturating the vagus with atropine is not to be expected.

**Clinical Observations.** With few exceptions the dose given in published cases has been one-fiftieth of a grain of atropine sulphate administered hypodermically. In one of Cushny's cases one-fiftieth of a grain was administered on one occasion and one-twenty-fifth of a grain on a second occasion, the ventricular rate rising to approximately the same level on the two occasions.<sup>4</sup> It has been felt that this single observation, from which it is argued that one-fiftieth of a grain is an adequate dose, constitutes insufficient evidence; in a preliminary series of observations upon three cases of auricular fibrillation, we gave separately and at suitable intervals doses of one-twentieth and one-tenth of a grain with a view to comparing the resultant ventricular curves. In two cases no difference was apparent; in the third case the rise with the one-tenth of a grain was appreciably the higher. In a second series of observations upon similar cases we have given one-fiftieth of a grain of atropine hypodermically, and have followed this by a further and intravenous injection at the height of the reaction to the first dose. The results are variable. In some few patients one-fiftieth of a grain given hypodermically appears to be adequate. More frequently, however, the rate rises further on the second dose (Figs. 2 and 3). The second rise amounts to as much as 10, 15 or 20 beats per minute. Through and through this added rise seems to be greater in patients who have previously been brought under the influence of digitalis. That is to be expected if we take the view that a dose adequate to cut out normal reflex vagal tone is not necessarily adequate to abolish this tone and also that which we might suppose added during the period of digitalis slowing.

Thus it would appear that the doses used to test the measure



of vagal tone in both the digitalized and undigitalized case have not always been adequate. The curves published by Mackenzie

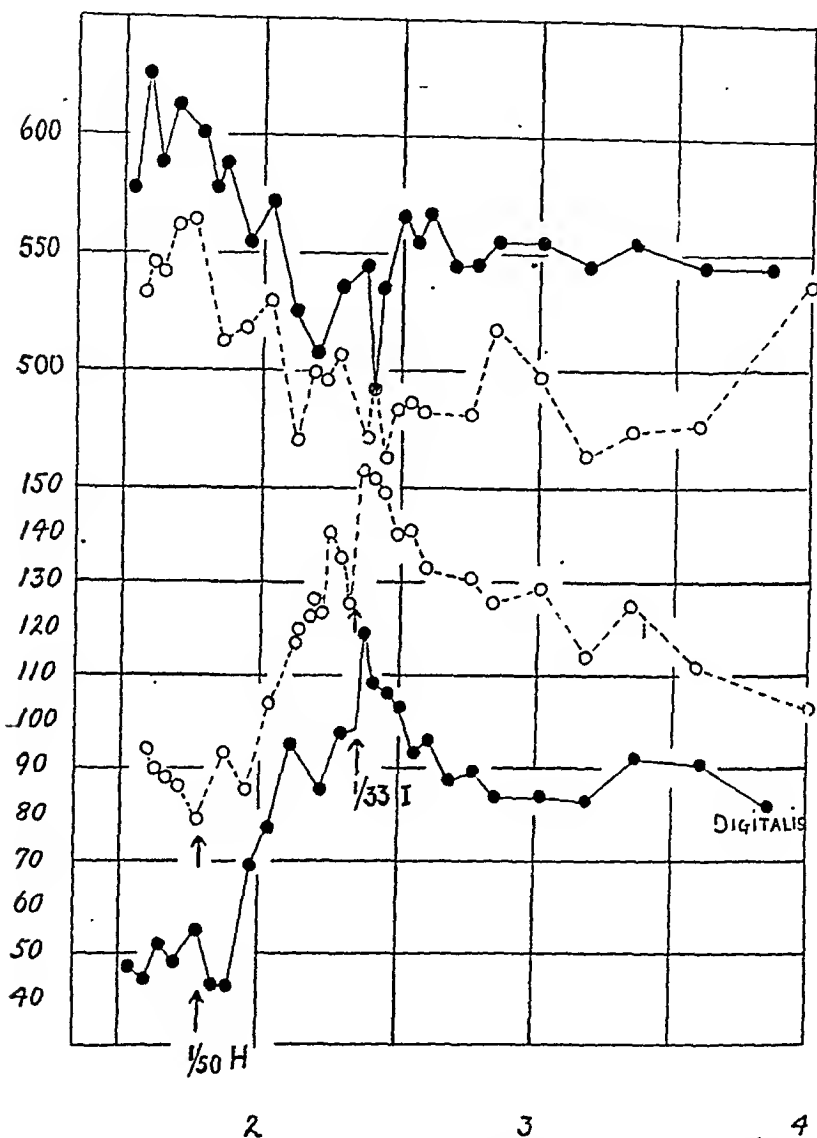


FIG. 2.—A chart of the auricular (upper curves) and ventricular rates (lower curves) in a case of fibrillation of the auricles. The curves were constructed from the patient while digitalis free (plain circles) and while under digitalis (black circles)  $7\frac{1}{2}$  drams of tincture had been taken in eight days. In both circumstances a hypodermic dose of  $\frac{1}{50}$  of a grain of atropine was followed by an intravenous dose of  $\frac{1}{33}$  of a grain.

and Cushny to illustrate the effects of abolishing vagal tone in digitalized patients cannot be regarded as wholly representative.

When fuller doses, single doses of one-tenth or of one-twentieth of a grain, or two doses bringing the total to one-twentieth of a grain, are administered, the rise is almost always above the level of the predigitalized rate (level *c*); often it is considerably above this

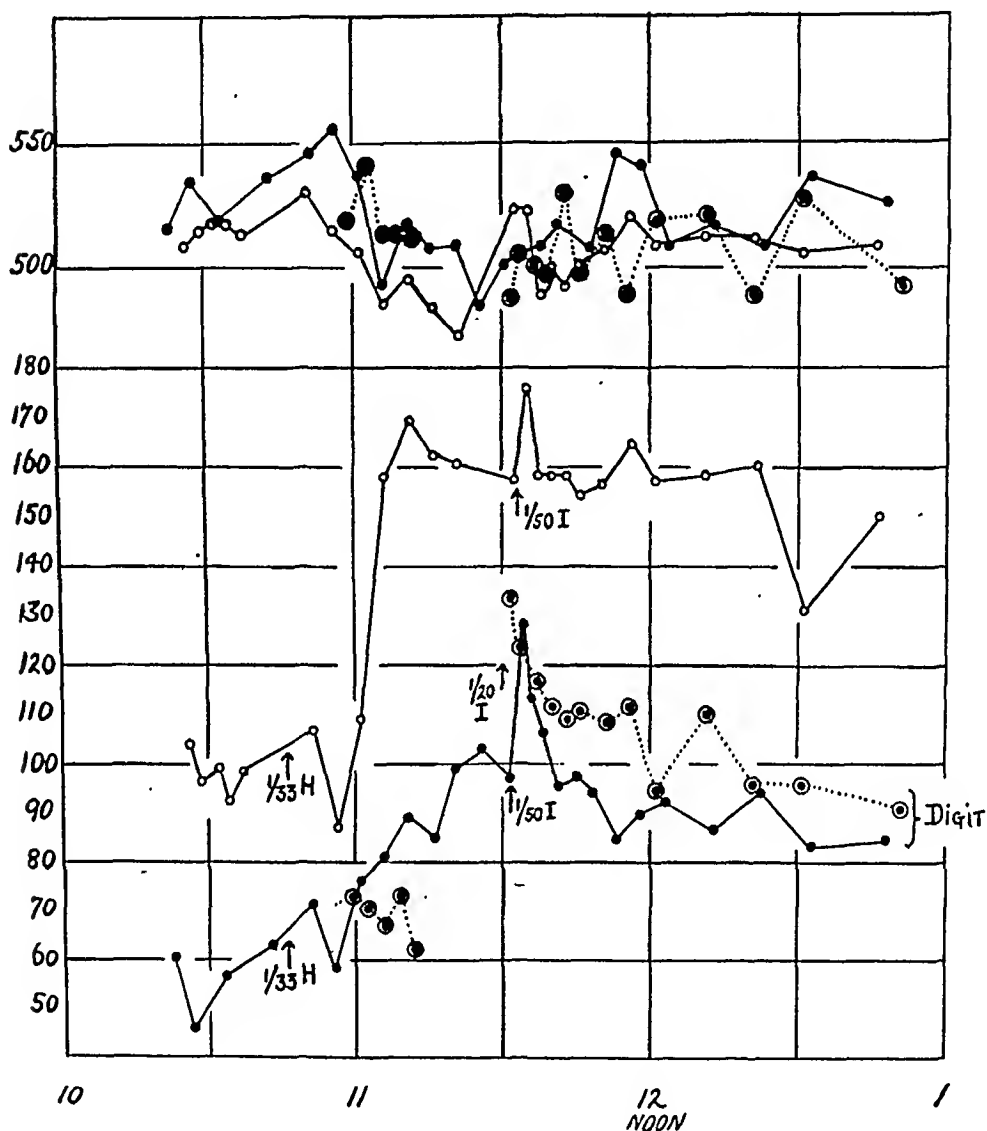


FIG. 3.—A similar chart from a second patient, to which has been added the curve produced by a single intravenous dose of  $\frac{1}{50}$  of a grain of atropine (double circles) while the patient was still under digitalis. The hypodermic injections in the case of the first curves were  $\frac{1}{33}$  of a grain and the intravenous doses were  $\frac{1}{50}$  of a grain.  $9\frac{1}{2}$  drams of tincture of digitalis had been taken in eleven days.

rate and exceptionally it may approach very closely to the rate obtained by the similar administration of atropine in the predigitalis stage (level *a*). Of the two procedures the former appears to be the more effective (Fig. 3), and presumably this is so, because when a hypodermic dose is given the reaction is not usually at its height for

twenty minutes, while if a similar intravenous dose is given, recovery usually begins before this time has elapsed. It is to be concluded therefore that the full effect of one-fiftieth of a grain is not always shown when the drug is given hypodermically. In one patient (Fig. 4) the original rate was 101, and atropine (one-twentieth of a grain) drove the rate to 232. The patient was now given full

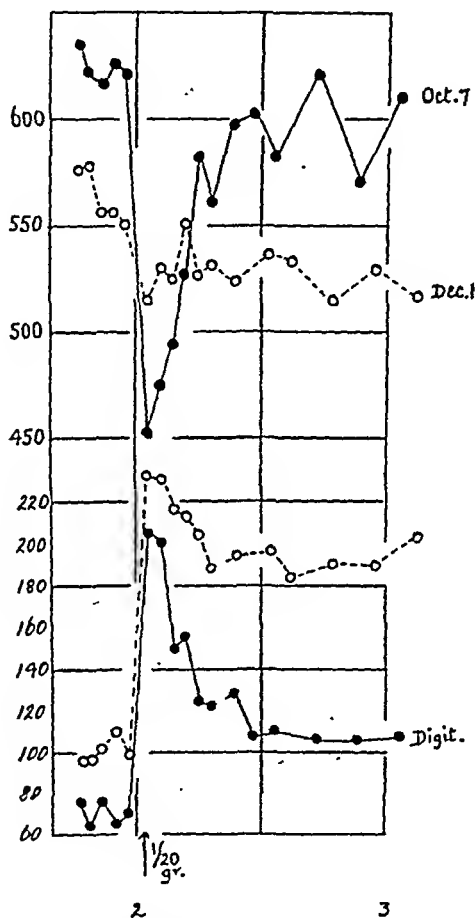


FIG. 4.—The effects of injecting  $\frac{1}{20}$  of a grain of atropine intravenously in a case of auricular fibrillation, before (plain circles) and after (black circles) bringing the heart under the influence of digitalis (9 drams of tincture in twelve days).

therapeutic doses of digitalis and the rate fell to 70; a dose of one-twentieth of a grain now increased the rate to 205. The first atropine rise was of 131 beats, the second of 135 beats. It is to be observed that the full rate of 232 was not attained at the second injection, consequently it cannot be concluded finally that the digitalis slowing in this case was of purely vagal origin; but it

can be concluded with some approach, may in large part the digitalis slowing was in large part vagal. The dose of atropine almost abolished, not only the rule that the also the preëxisting reflex tone. The difference is possible to the administration of digitalis was one of 31 beats. Through the difference in the maximal rates attained under atropine 27 beats. These two differences cannot reasonably be regarded as equivalent; the first, occurring while rates of 200 or over prevailed, is a minor difference as compared with that obtained at rates of 100 and under.

In view of such observations it seems reasonable to conclude that in some cases of auricular fibrillation, digitalis does exert an influence through the vagus and that in greater or lesser measure this increase of vagal tone is responsible for the ventricular slowing. It still cannot be concluded that in any patient, the fall of rate is wholly vagal; neither can it be said that an increased vagal tone is present in all these patients during digitalis slowing, observations are still insufficient to determine the percentage of cases so influenced or the precise degree in which the two factors are called into play. To embrace all cases of auricular fibrillation, our conclusion must remain tentative. We may sum up by stating that in the light of experimental and clinical observations it seems clear that digitalis exerts a twofold action, a direct and an indirect one, both of which decrease the facility with which impulses are conveyed across the *A-V* junction; both of which therefore reduce the rate of the responding ventricle. A similar conclusion has been reached by Robinson and Wilson<sup>14</sup> arguing from experimental data, and by Cohn<sup>1</sup> who argues mainly from clinical data. The proportion in which these two actions are exerted is probably variable in cases of fibrillation of the auricle; in some cases the vagal action appears to be the more conspicuous factor; in others, very probably, the direct action is predominant.

The importance of these conclusions will become more evident when we study the action of digitalis upon the auricle in auricular fibrillation.

**Action upon the Fibrillating Auricle.** Generally speaking it has been assumed that in cases of auricular fibrillation, exposed to the influence of digitalis, the auricular action remains constant, and that the whole effect upon the ventricular rate is localized in the junctional tissues. This is not strictly true; for the auricle is also affected. The action is not an entirely constant one, but in the majority of patients the oscillations recorded from the auricle are decidedly increased in rate (Figs. 2, 3 and 4). This change is studied in curves taken by means of direct leads from the chest wall, in which curves the electrical events in the auricle are represented in a comparatively pure form. Of 11 cases investigated, the oscillations showed no appreciable change of rate in 3 cases;

twenty minutes, while if a similar interval in the remaining 7 cases usually begins before this conspicuous rise of rate; in 2 cases the therefore that the full 80 beats per minute.

shown when the actual rise of rate due? To answer this question (Fig. 4) the origin understand the nature of auricular fibrillation.

grain) dromism, according to the theory we support, is the result of a continuously circulating wave in the auricle. The circus move-

ment controls the rate of the auricular oscillations, each oscillation corresponding to a complete auricular circuit. The time in which these circuits are completed actually depends upon two factors, (a) the length of the path followed and (b) the rate at which the wave travels. But the length of path is itself controlled by the length of the refractory period at any one point in the muscle and by the rate of conduction. Consequently we may say that the time in which a circuit is completed is controlled by two factors, namely, (1) the length of the refractory period and (2) the rate of conduction. As the rate of the oscillations per minute is due to the duration of individual circuits, it will be evident that the rate of oscillation is controlled by the same two factors.

A lengthening of the refractory period, by lengthening the path, will tend to increase the duration of each circuit and will slow the oscillations. Conversely, a shortening of the refractory period will tend to accelerate the oscillations.

Slowing of conduction will lengthen the circulation time and decrease the rate of oscillations; quickening of conduction, will increase the rate of the oscillations.

Now digitalis has two effects on the heart muscle. Insofar as it acts by increasing vagal tone it will reduce the length of the refractory period and it will tend to increase the rate of conduction. Thus, a vagal action of digitalis theoretically will reduce the time of circulation, will increase the rate of the oscillations. In experiment, vagal stimulation is well known to exert this influence upon the oscillations of a fibrillating auricle.<sup>10 15</sup>

On the other hand, digitalis, acting directly on the muscle, increases the length of the refractory period and retards conduction.<sup>11</sup> Theoretically, this direct action will increase the duration of the circulation time and slow down the oscillations. In anesthetized dogs, when a drug of the digitalis group is given, the vagal part of the drug's action is usually little in evidence, the chief action is a direct action. In such, the injection of the drug tends, as is expected, to slow the oscillations of the auricle which has been forced to fibrillate.

It is to be remarked that, when we are dealing with the rate of ventricular beating, both the direct and indirect actions of digitalis are exerted in the same direction, *i. e.*, toward ventricular slowing. But in the case of the fibrillating auricle, the direct and in-

direct actions are opposed to each other, and may in large part neutralize each other.

Because in actual observation we find it to be the rule that the auricular oscillations are increased in rate, it seems impossible to avoid concluding that the predominant action of the drug is through the vagus, so far at least as the auricle is concerned. The nature of the *A-V* block resulting from digitalis has been discussed and the observations of Cushny have been revised, mainly because, if his conclusion that this action is purely a direct one in cases of fibrillation of the auricle is correct, it would stand in conflict with what appears to be the inevitable conclusion in the case of the auricle itself. The revision of his work on the ventricle has led us to a conclusion which is compatible with the observations upon the auricle. Both the direct and indirect factors come into play. Just as in the case of the ventricle, so in the case of the auricle, the proportion between the direct and indirect actions is variable. In the case of the auricle, in virtue of the fact that the two effects of digitalis are manifested in opposite directions, it is an easier matter to ascertain their proportion than in the case with the ventricle, where the two effects are manifested in one and the same direction. An increase in the rate of the auricular oscillations, which appears to be the rule, signifies predominant vagal action; a decrease, which is sometimes seen, indicates a predominant direct action; unaltered rate indicates a balance between the two influences.

**Conversion of Flutter into Fibrillation by Digitalis.** In 1911 Mackenzie<sup>12</sup> reported two cases of paroxysmal tachycardia, in both of which digitalis appeared to exercise a beneficial effect. The tachycardia, in each case of obscure form, gave place to fibrillation of the auricles under digitalis, and subsequently a normal rhythm was resumed. In the first of these cases, historically the more important of the two, I took electrocardiograms from the patient during his period of tachycardia. These curves I was at the time unable correctly to interpret, but they were published in Mackenzie's paper.

In the following year I was able to report upon a similar case in which a long-continued tachycardia was converted by the action of digitalis into fibrillation of the auricles with a subsequent resumption of the normal rhythm;<sup>7</sup> and was able to identify the original tachycardia of this case with those previously reported by Hertz and Goodhart<sup>5</sup> and Jolly and Ritchie,<sup>6</sup> and termed by the latter writers "auricular flutter." The observations upon this case further enabled me in the same article to place a final and correct interpretation upon the case reported by Mackenzie; it became evident in the light of the new case that Mackenzie's case had also been one of flutter. A series of cases in which a similar

reaction to digitalis was observed was reported at a later date<sup>9</sup> and was soon followed by confirmatory observations by Ritchie and others.<sup>13</sup> The curious reaction, by which flutter of the auricle is converted to fibrillation, soon became well known and is now widely recognized. So far, however, it has not been explained.

The chief differences between clinical flutter and fibrillation, which have as yet been established, are that in the last condition the oscillations are more rapid and that they have not the regular incidence of those seen in flutter. According to our views the first difference may be interpreted to mean that the circuit movement is completed more rapidly, the second difference is due to irregular conduction in the case of fibrillation. What is the underlying cause of these differences? On this question it is still impossible to speak with certainty. The rapidity with which the circus movement is completed in fibrillation may be due either to more rapid conduction or to a shorter path.

It is very difficult to assume the first for several reasons. In general, the more rapidly an auricle beats, the slower will its tissue conduct, so that actually we should expect fibrillation to be associated with slower and not with faster conduction. If we were dealing with fibrillation in one patient and flutter in another, this argument would lose much of its force; but we have to face the fact that both flutter and fibrillation may occur as stable mechanisms in one and the same patient, under surrounding conditions which appear to be identical. Thus flutter, which has long been stable, may be converted into fibrillation by digitalis, and this may and often does continue as a stable mechanism, long after the action of digitalis has passed away. The reverse change may sometimes be accomplished by the use of quinidine. It is difficult to believe that the rate of conduction (at a given rate of beating) is permanently altered as an after-effect of administering one or other of the drugs. A second argument against faster conduction in fibrillation, is the irregularity of conduction, such irregularity being known to result when the conduction power is pressed to its utmost and is at its slowest. We are, therefore, probably correct in assuming that conduction is slower in the fibrillating auricle than in the fluttering auricle; but this difference fails to explain why the rate of oscillation is higher in fibrillation than in flutter; we turn to the alternative.

Does the difference consist in the length of path followed, the path being shorter in fibrillation than in flutter? Here again we have no direct and conclusive evidence, but there is some which is very suggestive. If we exclude faster conduction in fibrillation, then a shorter path may be due to shortening of the refractory period, it being assumed that in fibrillation the crest of the circulating wave always follows closely on the wake of retreat; in

these circumstances the actual length of path would be controlled by the length of the refractory period, the wave at once entering muscle in which recovery is expedited. This view, that the refractory period in fibrillation is less than in flutter, has been put forward already by Rothberger and Winterberg, for it is consistent with the known relation between refractory period and rate of beating, the former becoming of shorter duration as the rate rises.

The path in fibrillation may be shorter than in flutter for another reason. In the first condition we conclude that the gap between the crest of the wave and its wake is a very short one; and we come to this conclusion because conduction is irregular in fibrillation and the path varying. In flutter, on the other hand,

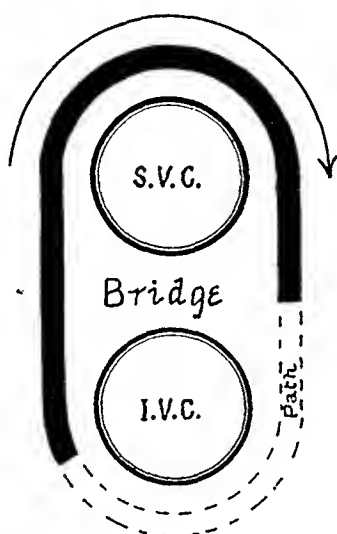


FIG. 5.—A diagram of circus movement around the superior and inferior vena cava, to illustrate how, when an appreciable gap exists, the wave may be unable to pursue a shorter course between the cavæ, unless the refractory period shortens. The diagram and its explanation suggest why the passage of flutter to fibrillation, or the reverse passage, should be an abrupt one.

the rate of conduction is constant and the path unvarying; this difference in the two mechanisms is consistent with the view that while the gap is short in fibrillation it is longer in flutter; the wave would then enter tissue in which an appreciable time for recovery has elapsed, whereby recovery of the tissue functions is carried further and to a more uniform point. Now a longer gap, other conditions being equal, would mean a longer path and a slower circulation time. Thus the essential distinction between fibrillation and flutter may consist in the length of the gap. This assumption would certainly seem to explain the observed differences between the two disorders.

If we accept this idea as a working hypothesis, it follows that



the path travelled in flutter is compulsory to this extent, that the head of the wave is unable to make a short cut and thus to approach more closely to its own wake. To explain this conception in more detail, imagine the wave in flutter to be circulating around the mouths of both superior and inferior vena cava (Fig. 5). Such a circulating wave may exist in a stable form although a considerable gap exists. It cannot take the short path between the two cavæ, for whenever its crest reaches this muscle bridge, it will find muscle on this cross-route refractory. But supposing that this is the state of affairs, and at a given moment the refractory period of the muscle shortens; the bridge may then be passed and the wave will then circulate, with a much shortened gap, around one or the other cava. The circulation time will decrease and, as a consequence, the refractory period will shorten a little more, tending to secure stability in the new mechanism, even when the original influence which shortens the refractory period is withdrawn. But as the gap is now smaller, conduction will tend to be more irregular and a little slower. In some such fashion it seems probable that the change from stable flutter to a more or less stable fibrillation may be produced.

Support is given to this argument by the change from stable fibrillation to stable flutter under quinidine. Hitherto, the significance of this change seems to have escaped notice. If the quinidine is given to these patients, a state closely resembling what we formerly termed flutter is always brought about, and this has been noted by several workers; but that is not the whole story. Usually the state produced is in reality impure flutter and this disappears invariably when the quinidine is withdrawn and its temporary effects on conduction and refractory period disappear. But in one patient in ten or more, pure flutter becomes established under quinidine; if now no further quinidine is given, the flutter does not disappear, it remains as a stable condition.

In the period of quinidinization, the refractory period is lengthening out and the rate of oscillations is falling. There comes a time when the reaction is at its height and the refractory period is at its longest; it is at this stage that pure flutter appears. We withdraw the quinidine and, as experience tells us, the refractory period recovers after a few (twenty-four to forty-eight) hours. Simultaneously any effect which the drug exerts on conduction must disappear. Thus, although both factors which tended to produce slowing of the oscillations disappear, little acceleration is apparent. A second and new condition of stability is reached. There is here little escape from the conclusion that the circuit contains a longer gap; such a gap must appear as recovery takes place without a corresponding speeding up of the movement. If similar doses of quinidine are repeated on this same patient when the flutter has

become quite stable, considerable doses may be given without appreciably affecting the rate of oscillation. There is some slowing, but this is minor in its degree and is to be attributed to the effect of the drug on conduction alone. It is comparable to the slight acceleration which occurs before the flutter becomes stable, a change due to improved conduction following withdrawal of quinidine. The delay of a pronounced fall in rate when the auricle is fluttering is due to the period occupied by closure of the gap by the lengthening refractory period.

Thus, we may conclude that one essential difference between flutter and fibrillation is that the gap is longer in the former.

We now return to the original question; and ask why digitalis converts flutter into the faster-moving fibrillation? Whether the reply is that it must quicken conduction, or whether the reply is that by reducing the refractory period it shortens the path upon which the wave circulates—and the latter is the more promising hypothesis—the explanation of its action will take the same direction; it will be necessary to assume that the quickening is due to a predominant action through the vagus nerve. Just as we explain an increased rate of oscillation in fibrillation itself consequent upon digitalis, so we explain the conversion of flutter in fibrillation; the vagal component of digitalis action will alone induce those changes in the muscle which are theoretically necessary to bring about the quickening which occurs. If you so desire, you may treat the question more upon the lines of direct observation. A material increase of vagal tone quickens the rate of experimental flutter and eventually may force it into fibrillation;<sup>13 15</sup> actually the effect of the direct action of a digitalis body upon flutter has not yet been observed, but we can predict that it would not quicken the movement, for in experiments on dogs, under certain conditions of anesthesia, in which the direct action is alone displayed and the auricles are fibrillating, quickening does not occur; on the contrary, slowing is often seen.

We need therefore have little hesitation in concluding that the conversion of flutter into fibrillation by digitalis is essentially vagal in origin.

**The Influence of Auricular Quickening upon Ventricular Slowing under Digitalis.** As stated, it has generally been assumed that when the auricles are fibrillating, the effects of digitalis upon the ventricle result simply from heart-block. This assumption is not in the strictest sense justified; for it is the rule to find that when the ventricle slows, the auricular mechanism also changes; in greater or lesser degree the movement quickens, and this quickening will exert some influence upon the rate of the ventricular response. Experiments bearing upon this point of view show that at fast rates of beating an increase of rate in the auricle tends in

itself to lower the rate of ventricular response; it favors block. The degree in which this influence is responsible for the ventricular slowing cannot be considered in detail on the present occasion. It must suffice if I say that, considering the relatively small change of rate which occurs in the auricle, we do not consider the influence to be a very material one at the rates prevailing.

It is to be noted also that atropine when given in cases of fibrillation produces a fall of auricular rate. This fall of rate will in a small measure favor a rise of ventricular rate, usually attributed entirely to removed vagal tone; the fall of auricular rate is usually small, and is not very materially different in digitalized and undigitalized cases; so that this effect has been neglected in the argument of this article. The magnitude of another factor in the action of atropine is less certain; in experimental fibrillation, if strophanthin is injected and produces a little slowing of the ventricle by a *direct action* rather than by a vagal action, an event which often occurs in dogs under full anesthesia, then a full dose of atropine does not increase the rate of the ventricle but may appreciably *decrease the rate*. If digitalis acted directly upon the muscle in man, and only directly, it seems probable that a similar decrease of ventricular rate with atropine would sometimes be seen in patients; actually this is not the case.

A final word completes what I have to say: It seems to us that the more we explore the facts and view them in the light of the theory of circus movement, as the fundamental cause of flutter and fibrillation, the more clearly is our whole knowledge of flutter and fibrillation illuminated. We cannot believe that the theory would be found to offer a reasonable interpretation of so many and such diverse phenomena unless it were fundamentally true.

#### REFERENCES.

1. Cohn: Jour. Am. Med. Assn., 1915, 65, 1527.
2. Cushny: Jour. Exper. Med., 1897, 2, 233.
3. Cushny: Jour. of Pharmae. and Exper. Therap., 1918, 11, 103.
4. Cushny, Marris and Silberberg: Heart, 1912-13, 4, 33.
5. Hertz and Goodhart: Quart. Jour. Med., 1908-9, 2, 213.
6. Jolly and Ritchie: Heart, 1909-10, 2, 177.
7. Lewis: Heart, 1911-12, 3, 279.
8. Lewis: British. Med. Jour., 1910, 2, 1670.
9. Lewis: Heart, 1912-13, 4, 171.
10. Lewis, Drury and Bulger: Heart, 1921, 8, 141.
11. Lewis, Drury and Hieseu: Heart, 1921, 9, 55.
12. Mackenzie: Heart, 1910-11, 2, 273.
13. Ritchie: "Auricular flutter," Edin. and London, 1914.
14. Robinson and Wilson: Jour. Pharmacol. and Exper. Therap., 1917-18, 10, 491.
15. Rothberger and Winterberg: Archiv f. d. ges. Physiol., 1914, 160, 42.
16. Traube: Gesamm. Beitr. z. Pathol. u. Physiol., 1871, 1, 190.

## THE SPLEEN AND DIGESTION.

## STUDY III. THE SPLEEN IN INANITION; THE EFFECT OF THE REMOVAL OF THE EXTERNAL SECRETION OF THE PANCREAS ON THE SPLEEN.\*

BY WILLIAM DEP. INLOW, M.S., M.D.,

FELLOW IN SURGERY, DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

THE spleen atrophies in inanition. Some observers have believed this to bespeak a part for the spleen to play in the temporary storing of protein food materials, analogous, in a way, to the part played by the liver in the storage of glycogen.

A functional interrelationship between the spleen and the pancreas, asserting itself especially during the digestive period, has been believed to exist by many investigators. This idea has found chief expression in the theory first put forward by Schiff, in 1862, and later championed by Herzen, that the spleen forms a product of internal secretion which can change trypsinogen into trypsin.

A striking simple atrophy of the spleen following complete removal of the external secretion of the pancreas has recently been reported by Sweet and Ellis. This atrophy, they believe, is greater than can be explained by the loss in body weight occurring under such circumstances. If this be true, it has direct bearing on the part of the spleen in digestion, and is suggestive of a specific pancreatic splenic interrelationship.

The investigation of the Schiff-Herzen hypothesis by determining the influence of splenectomy on pancreatic secretion has been reported in Study II of this series. In the present study further data on the splenic atrophy occurring in inanition will be presented, and the question of a suggested influence of the pancreas on the spleen will be approached by a repetition of the observations of Sweet and Ellis.

The spleen is an unusually variable organ. Its normal size in different animals is markedly fluctuant. Its weight in proportion to body weight varies not only in genera and species, but also in the individual. It changes its volume on slight provocation, and is highly susceptible to hypertrophy and atrophy. Therefore, conclusions drawn from changes in the size of this organ must be carefully checked.

In death from starvation the body weight of mammals is reduced two-tenths to four-tenths in the young and four-tenths to

\* Presented for publication July 1, 1921.

five-tenths in the adult (Fredericq and Nuel). The percentage losses of various tissues and organs in the cat are: fat, 97 per cent; spleen, 66.7 per cent; liver, 53.7 per cent; muscles, 30.5 per cent; blood, 27 per cent; intestines, lungs and pancreas, 17 per cent; bone, 13 per cent; central nervous system, 3.2 per cent; and heart, 2 per cent (Voit).

The effects of inanition in albino rats have been studied exhaustively by Jackson. He found apparently a decrease in weight of the spleen of 51 per cent in acute inanition and of 29 per cent in chronic inanition. He states, "That the spleen loses heavily during inanition, losing in relative as well as absolute weight has been found in man (Aschoff '11; Stschorstuy, 1898), pigeon (Chossat, '43), rabbit (Bowin, '90), and cat (Voit, '66; Sedlinair, '99), while a decrease less marked than in the whole body (relative increase) appears in the dog (Falek, '54) and in thin steers, compared with fat (data from Missouri Agricultural Experiment Station). Data from von Bechterew ('95) indicate a relative increase in the spleen of newborn kittens during inanition, but a decrease in puppies. These apparently conflicting statements are perhaps to be explained largely by the great variability of the spleen, making comparisons with controls uncertain. In addition, however, there is the possibility that the loss in the spleen may vary according to the character and stage of inanition. Thus Sasarew ('97) in the guinea pig found the greatest loss in weight of the spleen to occur in the middle period of inanition (second period of 10 per cent loss in body weight)."

An interesting necropsy on a tailor who refused all food and died on the sixty-third day has been reported by Mayers. The spleen was small and shrunken with a wrinkled capsule; it was pale and flabby and weighed only 53 gm. The body weight at death was about 80 pounds; he had lost 40.7 per cent of his original weight. If the spleen normally was of average weight it must have given up excessively of its substance. Microscopic examination of the organ revealed almost complete absence of the corpuscles, the distribution of many erythrocytes around the parenchyma and little evidence of the presence of the splenic sinuses.

The histologic changes occurring in the spleen of the cat and of the guinea pig in acute starvation have been studied by Jolly and Levin. They found a thinning of the pulp cords and a reduction in the number of lymphocytes. The venous sinuses were often filled with large phagocytic cells stuffed with erythrocytes.

The observation that an excessive shrinkage of the spleen occurs when the external function of the pancreas is removed was reported in a brief communication by Sweet and Ellis in 1915. They resected the duodenal portion of the pancreas in dogs, or ligated the pancreatic ducts, or cut them with the interposition of omentum between the gland and the gut. Thus the internal function of the

pancreas was still provided for and glycosuria did not develop. The animals had voluminous fatty stools, and at first lost weight rapidly; however, after several months they reached a stationary weight or even gained slightly. The change noted in the spleen consisted apparently of a simple atrophy, and was marked after three days. Control experiments in animals with equal loss of weight were not performed.

Sweet has suggested that there may be a possible surgical bearing of this relation between the pancreas and the spleen. He cites the report of Musser of an acute anemia in four of eight cases of acute pancreatitis. In view of the generally accepted relation of the spleen to the blood, he considers his finding of an acute splenic atrophy under the conditions cited as suggestive of an explanation of Musser's report of acute anemia, and as furthermore suggestive of the importance of clinically following the blood picture in cases of suspected or proved acute pancreatitis.

Animals deprived of sustenance are obliged to draw on their own storehouses and their own tissues for food. Yet dearth of aliment not alone leads to inanition, for non-assimilation, even though food is taken in the greatest of plenty, attains a similar end. If pancreatic juice is excluded from the intestine there is a marked diminution in the absorption of nitrogen and fat, as has been demonstrated by Pratt, Lamson and Marks. This results in an immediate disturbance in metabolism with loss in body weight. May not then the dwindling of the spleen in animals in which the external function of the pancreas has been removed be merely the expression of the ease with which this organ gives excessively of its substance when the body labors under nutritional deficiency? May it not be merely the atrophy of the spleen of inanition?

Most comparative studies of the changes in weight of organs have been made by checking the findings of the abnormal states with the findings under normal conditions in individuals of the same species. In the case of the spleen this method is fraught with great error attributable to the protein habits of this most mysterious and changeable organ. Hence, in the gathering of experimental data in answer to the above question complete observations should be made on one and the same animal in each instance.

**Experimental Methods and Data.**—In adult dogs complete removal of the external secretion of the pancreas was obtained by resection of the duodenal portion of the gland with tying off securely the severed ends of the remaining pancreas after the manner of Sweet and Ellis or by double ligation of the pancreatic ducts. Observations were also made on dogs with pancreatic fistulas complicated in most cases by pancreatitis. These animals were kept on full diet. As controls, dogs were fed a half-day's ration every third day and fasted in the interval. The size of the spleen was determined

at the start and at the end of every experiment. Microscopic sections of the spleen and pancreas, and often also of other organs, were made.

The initial splenic weight was determined as follows: Measurements of the total length, of the width of the head and of the tail, and of the thickness of the spleen were made by a movable centimeter scale. For the head the measurement of greatest width was taken; for the tail a transverse line was drawn through a point on the longitudinal axis of the organ (this point was placed at such a distance from the caudal extremity as to represent a certain fraction of the total length of the spleen); and for the thickness, a line was drawn at the middle of the gland running from the hilus perpendicularly to the broad free splenic surface.

The body, and thus the major portion of the spleen of the dog, most nearly resembles a rectangle in outline; the head is increased in width at one side and tapers at the tail; a cross-section at most points is triangular with the apex at the hilus. Therefore, because of its form, the exact computation of the volume of the spleen is not feasible from the measurements taken. However, since weight, the final value of which is easily determined at necropsy, serves our purpose even better than volume, the use of proportion will permit us to make an approximate estimation of the initial weight of the spleen without knowing the exact splenic volumes.

If changes in specific gravity are disregarded for the time being the proportion as follows will hold:  $x : a :: y : z$ . (in which  $x$  = initial splenic weight,  $a$  = final splenic weight,  $y$  = initial splenic volume and  $z$  = final splenic volume).\* Since the splenic volumes are unknown as well as the value of  $x$ , we may substitute for  $y$  and  $z$  in the proportion the volumes of similar rectangular parallelopipeds (for the volumes of similar irregular solids are proportional to the similar regular parallelopipeds most nearly approximating their own shape) which can be determined from the measurements given. In the present study the lengths and thicknesses of the spleens and the means of the widths of their heads and tails have been taken for the dimensions of the parallelopipeds. If then  $b$  is taken as the volume of the parallelopiped corresponding to the initial size of the spleen and  $c$  as that corresponding to the final size, these known values may be substituted for  $y$  and  $z$  in our proportion, which will then read:  $x : a :: b : c$ .

However, the values thus determined for  $x$  do not take into account changes in specific gravity. In three of the spleens in this series the specific gravity (determined by Hammerschlag's method) was found to be approximately 1.060 for the normal and 1.070 in inanition. There were but small changes from this latter figure with lesser or greater lengths in the periods of loss of weight,

\* The author is indebted to Mr. H. O. Stearns of the Mayo Clinic for suggestions regarding the mathematical procedure used in this method.

the spleen evidently losing very rapidly of its fluids in acute inanition. Therefore in the values given for the initial weights of the spleens this correction for change in specific gravity has been made, that is, the initial weights have been multiplied by the factor 0.99.

**Histologic Changes.**—*The Spleen.* The histologic changes in the spleen, found in these experiments, appeared similar, regardless of the procedure employed, so long as loss of body weight occurred. In the instances in which the experiments were prolonged for fifty days or longer the microscopic picture seemed identical in the fasting animal and in the animal deprived of the external secretion of the pancreas. Therefore the histologic findings will be given in one description.

Changes in the spleen were observed as follows: The capsule was shrunken, wrinkled and much decreased in width; its fibrous tissue strands were compact, giving at times an almost hyaline appearance; nuclei were less abundant and the few scattered lymphocytes usually seen were absent. The shrinkage in the splenic septa was not so noticeable. The parenchyma, however, was quite decreased in amount, so that comparatively the septa stood out as more numerous than normal. In the splenic pulp the cells often were packed almost as closely as in the normal Malpighian corpuscle. The tissue spaces were largely obliterated. The cytoplasm of the pulp cells and pulp supporting tissue had largely disappeared, and the nuclei, closely crowded, chiefly remained. The splenic sinuses, although diminished in size, often stood out clearly; the amount of blood they contained was less than that seen in a normal section. The number of lymphocytes outside the Malpighian corpuscles was markedly decreased; cells of large type predominated. The Malpighian corpuscles themselves and their germinal centers seemed more definitely delimited than usual. The larger bloodvessels of the gland appeared but little altered. There was constantly more free blood pigment in the pulp than normal.

The degree of these changes seen in the spleen was roughly proportional to the length of the experimental period and to the acuteness with which loss of body weight occurred. The changes themselves were such as those ascribed to a simple atrophy of the gland.

*The Pancreas.* In the instances in which a partial pancreatectomy was performed, or the pancreatic ducts were ligated, varying degrees of destruction of the pancreatic acini and their replacement by connective tissue occurred, depending on the length of time of removal of the external function of the pancreas with the resultant obstruction of the pancreatic ducts. In the most acute experiments merely a decrease in the clearness of the staining reactions or a beginning necrosis was seen. In the prolonged



experiments very little acinar tissue was left. The pancreatic ducts and their larger ramifications were in most instances dilated to three or four times their normal size.

In those cases in which pancreatic fistulas were performed without infection no damage to the acinar tissue occurred. However, generally a complicating purulent pancreatitis, of varying intensity and acuteness, was present.

**Protocols.**—All operative procedures on the experimental animals were performed under ether anesthesia with the employment of



FIG. 1.—D 537. Ligation of pancreatic ducts. Normal spleen at the beginning of the experiment. Photomicrograph  $\times 50$ .

sterile technic. In none of the dogs in which the external function of the pancreas was removed did glycosuria appear; all, however, had fatty stools.

**Ligation of Pancreatic Ducts.**—D 537, a male mongrel in good condition. April 23, 1920, both pancreatic ducts were doubly ligated and divided. The animal gradually lost 2.6 kg. during the first month and then became stationary in weight till the ninth week, when symptoms of inanition appeared. From this time there was a rapid and progressive loss. July 27 the dog was killed

by etherization. At necropsy very little pancreatic tissue could be found. The pancreatic ducts were not dilated. Histologically the pancreas consisted almost entirely of connective tissue, although a few areas were still present containing islets of acinar tissue (Figs. 1, 2 and 3).

**Resection of Duodenal Portion of Pancreas.**—D 648, a male mongrel in good condition. April 30, 1920, the duodenal portion of the pancreas was resected. The animal made an excellent recovery and maintained its weight for one week. During the next three



FIG. 2.—D 537. Ligation of pancreatic ducts. Spleen at the end of the experiment. Photomicrograph  $\times 50$ .

weeks there was a loss of only 1 kg.; following this there was a progressive and steady decline in weight. July 22, the dog was killed by etherization. At necropsy all the tissues seemed to be anemic; save for a few small islets the pancreatic glandular tissue had disappeared. The pancreatic ducts were distended to about six times their normal size. It was difficult to identify the splenic sinuses histologically; they appeared almost obliterated. The pancreas was fibrous.

D 649, a male mongrel in good condition. April 30, 1920, the

duodenal portion of the pancreas was resected. The skin incision became infected and did not heal. Later, distemper developed. The dog lost weight rapidly and progressively from the time of the operation. It was killed by etherization May 17. At necropsy a diffuse pancreatic fat necrosis was found. Histologic examination revealed much free blood pigment in the spleen. The pancreas was necrotic. There were areas of bronchopneumonia in the lungs.

D 661, a male poodle in fair condition. May 7, 1920, the duodenal portion of the pancreas was resected. The animal recovered



FIG. 3.—D 537. Ligation of the pancreatic ducts. Pancreas showing fibrosis and remaining islets of acinar tissue at the end of the experiment. Photomicrograph  $\times 50$ .

well, but lost weight steadily until the last eleven days before death, when the weight became stationary. July 2, the dog was killed by etherization. At necropsy very little pancreatic tissue was found. The pancreatic ducts were dilated to about four times their normal size. The section of the spleen removed at operation for histologic study contained a number of large multinucleated cells. Only a few of these could be seen in the section from the specimen removed at necropsy. There was a marked collection of blood pigment in the pulp of the atrophic spleen. In the pancreas a small amount of acinar tissue was left in islets (Figs. 4 and 5).

D 698, a female terrier in good condition. May 27, 1920, the duodenal portion of the pancreas was resected. The spleen was large for the size of the dog and grossly pathologic; it was cirrhotic and contained numerous small infarcts. The animal developed distemper almost immediately and was killed by etherization May 31. At necropsy marked purulent conjunctivitis, rhinitis and tracheobronchitis were present. The abdominal wound was infected superficially and showed no evidence of healing. There was a slight degree of pancreatic fat necrosis in the omentum

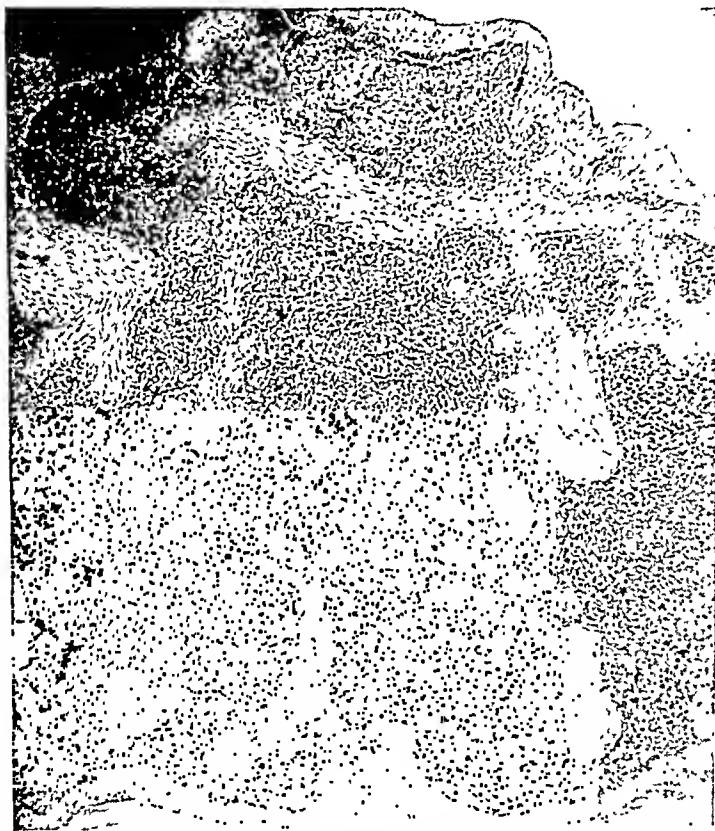


FIG. 4.—D 662. Partial pancreatectomy with loss of external secretion of pancreas. Spleen at the end of the experiment. Photomicrograph  $\times 50$ .

around the ends of the severed pancreas. The pancreas itself was indurated as if it had been in fixing fluid. There were no findings to explain the original pathologic condition of the spleen. Histologic examination did not reveal changes in the spleen or the pancreas.

**Pancreatic Fistula Complicated by Infection.**—D 720, a female mongrel in excellent condition. June 12, 1920, a one-stage operation for pancreatic fistula was performed. An accessory spleen 0.45 cm. in diameter was found in the omentum 7 cm. from the hilus of the major spleen. The animal refused all food, and milk fed

through the stomach tube was vomited. An irritative pancreatic secretion appeared and the animal thus continuously lost large quantities of pancreatic juice. The last four days preceding death, which occurred July 2, a marked inanition supervened. At necropsy a non-purulent infection involving the transplanted portion of the pancreas was found. A large amount of subcutaneous fat was still present, but the animal was extremely dehydrated. The accessory spleen was atrophic with a diameter of 0.34 cm., thus having lost 43 per cent in volume.



FIG. 5.—D 661. Partial pancreatectomy with loss of external secretion of the pancreas showing destruction of acinar tissue with fibrosis and a dilated pancreatic duct. Photomicrograph  $\times 50$ .

D 743, a male bull terrier in fair condition. June 19, 1920, a one-stage operation for pancreatic fistula was performed, with ligation of the minor pancreatic duct. The wound became infected superficially and was slow in healing; the animal steadily lost weight and became extremely emaciated, and there was a marked continuous irritative secretion of juice from the fistula. The animal died July 14. At necropsy a purulent pancreatitis was found.

TABULATION

Animal.	Duration of experiment, days.	Initial body weight, kg.	Final body weight, kg.	Total change in weight, kg.	Length of spleen, cm.		Width of spleen, cm.				Thickness of spleen, cm.		Initial weight of spleen (approximate), gm.	Final weight of spleen, gm.	Spleen: initial percentage of body weight (approximate).	Spleen: final percentage of body weight.	Percentage of change of body weight.	Percentage of change of weight of spleen. (approximate).	Procedure.
					Initial.	Final.	Head.		Tail.		Initial.	Final.							
							Initial.	Final.	Initial.	Final.									
D 698	4	9.5	8.5	-1.0	15.8	13.8	4.1	3.3	3.5	3.3	1.3	1.2	52.3	37.0	0.550	0.435	-10.5	-29.8	Partial resection of pancreas (distemper).
E 129	4	19.6	16.8	-2.8	16.0	15.5	7.1	4.6	4.0	3.3	1.3	0.8	73.2	32.6	0.373	0.194	-14.3	-55.5	Pancreatic fistula (peritonitis).
E 131	15	10.0	7.6	-2.4	14.2	14.2	5.3	4.0	4.0	2.3	0.8	0.7	30.5	18.3	0.305	0.240	-24.0	-40.0	Pancreatic fistula (pancreatitis).
D 649	17	7.0	4.8	-2.2	11.1	10.6	3.1	2.6	2.6	2.1	0.7	0.4	14.5	8.0	0.207	0.166	-31.3	-45.0	Partial resection of pancreas (pancreatic fat necrosis; distemper).
D 730	20	11.7	8.2	-3.5	10.9	9.8	3.8	2.1	2.9	1.8	1.1	0.6	29.0	8.5	0.248	0.104	-29.9	-70.7	Pancreatic fistula (pancreatitis).
D 743	25	19.6	12.4	-7.2	17.6	15.8	6.1	4.5	4.0	2.8	1.4	1.1	72.3	33.8	0.369	0.273	-36.7	-53.0	Pancreatic fistula; ligation of minor pancreatic duct (pancreatitis).
D 130	28	10.2	10.6	+0.4	13.8	15.2	4.8	4.6	4.0	3.4	1.0	1.0	28.47	28.5	0.279	0.269	+3.9	+0.1	Pancreatic fistula.
D 876	51	9.4	6.4	-3.0	11.9	9.8	5.9	4.0	2.0	1.7	0.8	0.6	20.0	10.0	0.213	0.156	-31.9	-60.0	Fasting.
D 875	51	13.0	7.0	-6.0	11.7	8.0	6.7	4.3	2.5	1.6	2.2	0.7	56.4	7.8	0.433	0.111	-46.2	-86.1	Fasting.
D 661	55	13.8	7.8	-6.0	17.0	10.4	4.5	2.3	4.0	2.0	1.4	0.7	70.0	10.5	0.508	0.350	-43.5	-85.0	Partial resection of pancreas.
D 648	82	14.1	8.6	-5.5	11.4	8.6	5.2	4.5	3.1	2.1	1.0	0.5	29.7	9.0	0.248	0.105	-39.0	-70.0	Partial resection of pancreas.
D 537	96	17.6	9.7	-7.9	14.1	11.4	4.8	3.0	4.4	2.4	1.0	0.8	40.5	16.0	0.287	0.165	-44.5	-60.5	Ligation of pancreatic ducts.

E 131, a male mongrel in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The wound became infected and a continuous irritative secretion of pancreatic juice appeared. The animal refused food and lost weight rapidly. Death occurred December 22. Pancreatitis was found at necropsy. The initial specific gravity of the spleen in this instance was 1.061, that at death 1.073.

E 129, a male shepherd in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. The



FIG. 6.—D 875. Fasting. Spleen at the end of the experiment. Photomicrograph  $\times 50$ .

animal became extremely ill and died December 11. At necropsy a generalized peritonitis with a small amount of sanguinopurulent fluid in the peritoneal cavity was present. The initial specific gravity of the spleen in this instance was 1.062; that at death, 1.070.

**Fasting.**—D 875, a male bull terrier in good condition. August 6, 1920, the abdomen was opened and measurements of the spleen taken. The animal was then fed a half-ration every third day and fasted in the interval. Save for a slight gain at the end of one and a half weeks and a stationary period from the seventeenth to the twenty-sixth day the animal lost weight progressively. September

28, splenectomy was performed. Death occurred two days later, probably as a result of the operation and the dog's weakened condition. A section of the spleen at the first operation had many multinucleated giant cells, and free blood pigment was present in the pulp. A section of the spleen at its removal showed changes identical with those occurring after removal of the external secretion of the pancreas. The amount of free blood pigment was increased. No multinucleated giant cells could be found (Fig. 6).

D 876, a male mongrel in good condition. August 8, 1920, the abdomen was opened and the spleen measured. The animal was then fasted in a manner similar to D 875. The weight from the twelfth to the twenty-sixth day remained constant, but steadily decreased at all other periods. September 28, splenectomy was performed. The dog made a good recovery. The histologic changes in the spleen were those of a simple atrophy.

**Uncomplicated Pancreatic Fistula.**—E 130, a female mongrel in good condition. December 7, 1920, a one-stage operation for pancreatic fistula was performed. Recovery was excellent and the wound healed without infection. Secretion of juice from the fistula was normal. The animal was carefully fed and gained weight slightly. January 4, 1921, the spleen was removed, without incident. The initial specific gravity of the spleen was 1.061; that at the time of splenectomy was 1.060. The splenic measurements remained practically the same.

**Discussion.**—The size of the spleen of the dog varies greatly; in this series of experiments it fluctuated between 0.2 and 0.55 per cent of the body weight, with an average of about 0.3 per cent.

The data submitted justify the conclusion that the spleen loses markedly in weight in inanition and are in general corroborative of the findings of other investigators. The loss in the weight of the spleen is out of all proportion to the decrease in body weight, being almost three times as great as a maximum in extreme cases of acute inanition, and approximately twice as great in cases of less acute.

The removal of the external function of the pancreas by ligation of the pancreatic ducts or resection of the duodenal portion of the gland likewise leads to an excessive decrease in the size of the spleen. This finding thus confirms the observations of Sweet and Ellis. However, the shrinkage of the spleen under these conditions can be explained as due to the inanition resulting from the exclusion of the pancreatic juice from the intestine, and does not require for its elucidation the postulation of a specific pancreatic splenic interrelationship.

The loss of weight of the spleen in relation to the loss of body weight in these experiments is shown graphically in Figure 7. It will be noted that the greatest loss of weight both of the body and of the spleen occurs within the first month. The diminution of



the weight of the spleen is especially rapid during the first few days of inanition. The chart indicates also how markedly the percentage splenic weight fluctuates from the normal in contradistinction to the percentage body weight, which shows relatively little such fluctuation.

That the marked atrophy of the spleen under the experimental conditions of this study is nothing more than the mere expression of the disproportionate share of the gland in the general loss of weight is shown by a comparison of the experimental results in the cases of Dogs D 661 and D 875, the former representing a

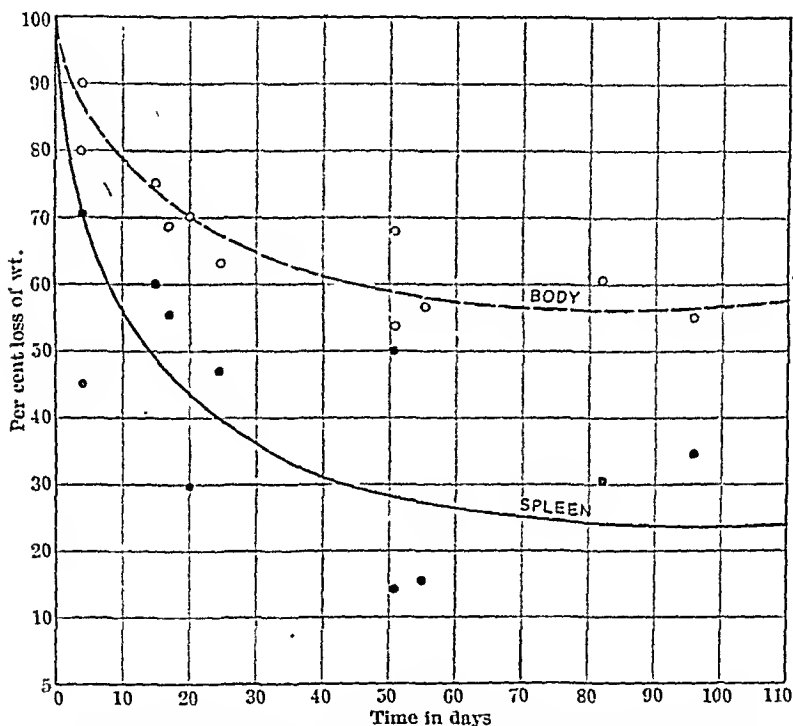


FIG. 7.—Graphs illustrating the percentages of losses of weight of the body and of the spleen in relation to the length of the inanition period. (See table.)

partially pancreatectomized animal and the latter a control under starvation. Both animals weighed approximately 13 kg. and lost about 45 per cent of their body weight within a period of fifty days, whereas their spleens each lost about 85 per cent of their original weight. These are the most marked losses in weight obtained, but the experiments are in every sense parallel (Fig. 8).

The observations made on Dog E 130, with a pancreatic fistula, show that even if an animal loses over half the amount of pancreatic juice secreted and yet maintains a stationary body weight there is no loss in the size of the spleen.

Data were collected on dogs with pancreatic fistulas complicated by infection in order to study the effects of pancreatitis on the spleen, since Sweet has suggested that in this direction may be the explanation of the anemia of pancreatitis found in certain cases by Musser. Save for a more acute and marked loss in weight of the animals, caused doubtless by the toxemia of the infection and by the dehydration and loss of alkali resulting from the constant secretion of large quantities of juice from the fistula, the results obtained in these cases seem entirely comparable with those obtained in the cases of fasting and removal of the external secretion of the pancreas.

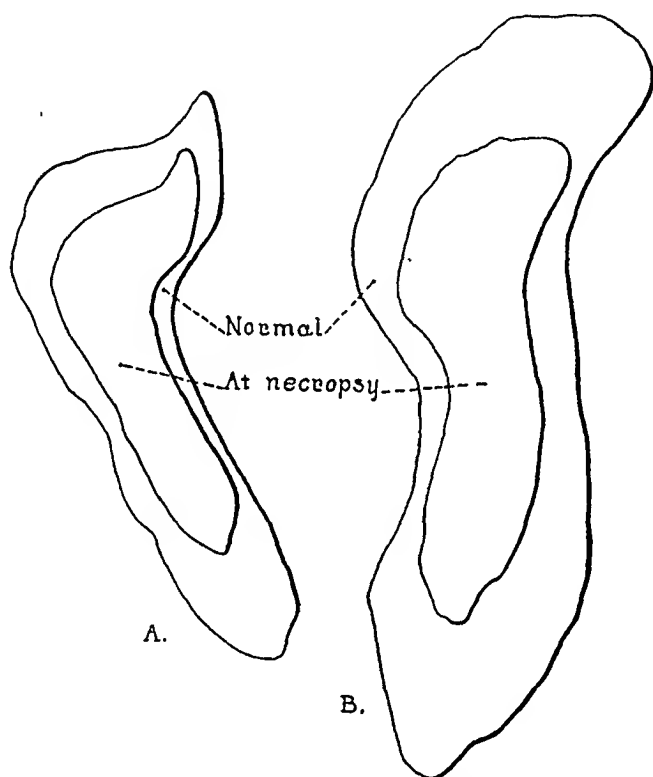


FIG. 8.—Marked shrinkage of the spleen. *A*, in fasting (D 875); *B*, following partial pancreatectomy with loss of external secretion of pancreas (D 661).

It might be expected that in acute infections, for example, the cases of acute pancreatitis, of distemper, and of peritonitis, given in the protozoals the toxemia would cause enlargement of the spleen in the form of acute splenic tumor. Yet in these infections the animals refuse food and assimilate poorly what is taken. Marked loss of weight develops and, as shown in these experiments, the spleen diminishes in size.

Of what significance is this extraordinary atrophy of the spleen in inanition? Why must this organ, next to the inert tissue, fat, give so readily and lavishly of its substance for the nourishment of its host? Does such lavishness imply that this unique gland

can play but a slightly important part in the general economy and physiology of the organism; or may it still be that the spleen can give heavily of its substance in famine and yet remain a valuable organ with divers and sundry useful though little known functions? Or does the spleen with specific purpose aid in the garnering and temporary storing of protein food materials in order that it may dole out sustenance when the body is hard put?

#### BIBLIOGRAPHY.

1. Fredericq, L., and Nuel, J. P.: *Éléments de physiologie humaine à l'usage des étudiants en médecine*. Grand and Paris, Hoste, 1893, 667 pp.
2. Herzen, A.: Ueber den Einfluss der Milz auf die Bildung des Trypsins. *Arch. f. d. ges. Physiol.*, 1882-1883, 30, 295-307.
3. Herzen, A.: Aelteres, Neues, und Zukünftiges über die Rolle der Milz bei der Trypsinbildung. *Arch. f. d. ges. Physiol.*, 1901, 84, 115-129.
4. Inlow, W. D.: The Spleen and Digestion. Study II. The Spleen and Pancreatic Secretion. *AM. JOUR. MED. SC.*, 1922, 164, 29-44.
5. Inlow, W. D.: A Technic for the Establishment of a Permanent Pancreatic Fistula with the Secretion of Inactive Proteolytic Ferment. *Jour. Lab. and Clin. Med.*, 1921, 7, 86-90.
6. Jackson, C. M.: Effects of Acute and Chronic Inanition upon the Relative Weights of the Various Organs and Systems of Adult Albino Rats. *Am. Jour. Anat.*, 1915, 18, 75-116.
7. Jolly, J., and Levin, S.: Sur les modifications histologiques de la rate à la suite du jeune. *Compt. rend. Soc. de biol.*, 1912, 72, 829-831.
8. Meyers, A. W.: Some Morphological Effects of Prolonged Inanition. *Jour. Med. Res.*, 1917, 36, 51-77.
9. Pratt, J. H., Lamson, P. D., and Marks, H. K.: Effect of Excluding Pancreatic Juice from the Intestine. *Tr. Assn. Am. Phys.*, 1909, 24, 266-281.
10. Schiff, M.: Ueber die Function der Milz. *Schweiz. Ztschr. f. Heilk.*, 1862, 1, 201, 397.
11. Sweet, J. E.: The Surgery of the Pancreas. *Internat. Clinics*, 1915, 25s., 4, 293-357.
12. Sweet, J. E., and Ellis, J. W.: The Influence upon the Spleen and the Thyroid of the Complete Removal of the External Function of the Pancreas. *Jour. Exper. Med.*, 1915, 22, 732-738.
13. Voit, C.: Quoted by Fredericq and Nuel.

### GASTROSPASM: A CLINICAL AND ROENTGENOLOGICAL STUDY.<sup>1</sup>

BY I. W. HELD, M.D.,

NEW YORK,

AND

J. ROEMER, M.D.,

PATERSON, N. J.

EVEN before the roentgen-ray era local gastrospasm, especially such that occurs at the entrance and exit of the stomach (cardio-

<sup>1</sup> Read in part by J. Roemer, M.D., at the annual meeting of the New Jersey State Medical Society, June 15, 1920.

and pylorospasm respectively), was clinically known. In 1881 Strumpell called attention to what he named esophagismus, describing the spindle-shaped dilatation of the esophagus, and Mikulicz demonstrated it by his esophagoscope. Spastic pylorospasm in the adult was first described by Kussmaul and in the infant by Still. Complete gastrospasm was mentioned by anatomists and physiologists (Home, Tiederman and Gmelin) in the early part of the nineteenth century. Local segmentation of the stomach was mentioned by Retzius, who found it at the autopsy of a man who died suddenly during the stage of digestion.

Williams described the human stomach to possess three natural physiological constrictions: (1) Near the cardia which corresponds to the incisura cardica (His); (2) in the middle of the stomach; (3) at the antrum. Banchi, Cunningham and Orr mentioned the physiological pseudo-hourglass constrictions. Buedinger found during a laparotomy a spastic hourglass opposite the seat of the ulcer. Simmonds found at autopsy an hour-glass stomach with no demonstrable lesion in any part of the stomach. Becky injected the human stomach, soon after death, with formol and often found contraction phenomena corresponding to an hourglass. Recently, Waldvogel<sup>2</sup> demonstrated by inflation of the stomach that gastrospasm is not an infrequent occurrence.

Whereas this historical introduction serves to show that the subject is not new, we must not lose sight of the fact that its clinical importance and the possibility of diagnosing it correctly are the achievements of the roentgen-ray study by means of the contrast meal. It must be emphasized that gastrospasm as a sign is demonstrated by the roentgen-ray, but its diagnostic significance can only be interpreted by a complete clinical study.

Gastrospasm was aptly divided by Holzknecht and Luger<sup>3</sup> into regional, circumscribed and total. Regional gastrospasm may occur in any part of the stomach; the most common locations are at the cardia and pylorus.

**Cardiospasm.** Although cardiospasm primarily belongs to the cardiac end of the esophagus, its relation to gastric diseases and its symptomatology are so purely gastric that brief mention of it must be made here. We understand by cardiospasm a spastic contraction of the cardiac end of the esophagus, of shorter or longer duration, sometimes lasting for weeks and even months and leading to dilatation above the contraction. From an etiological standpoint cardiospasm is in the great majority of cases purely functional. This is easily understood when we recall that the propulsion of food from the esophagus into the stomach is mostly controlled by the autonomic nervous system. That is why the esophagus can be entirely stripped of its musculature if the mylohyoid muscle remains and

<sup>2</sup> München. med. Wchnschr., 1911, No. 2.

<sup>3</sup> Mitteilungen auf dem Grenzgeb., 1913, p. 669.

the nerves be intact, without disturbing the passage of food from the esophagus to the stomach.

This is not the place to enter into a detailed discussion of the physiology of deglutition and of the epoch-making and conclusive experimental work of Kroeneker, Meltzer, Cannon, Krauss and others; but some mention must be made of the innervation of the lower end of the esophagus and cardia.

The chief nerve supply of the motor function of the lower end of the esophagus and cardia is derived from the vagus. The influence of the sympathetic nerve fibers on the lower end of the esophagus is today also conceded. The existence, however, of intrinsic nerves of the lower esophagus and cardia able to carry out the function independent of whether or not the chief nerve supply is intact was demonstrated by Cannon. These nerves are important when they are called upon to take up the expulsion of the food from the lower part of the esophagus to the stomach and when there is obstruction at the cardia on account of an organic disease of the vagus. We thus see the important role played by the vagus and its allied nerves in controlling the act of deglutition. The disturbance of deglutition due to organic affection of the vagus and its allied nerves, either centrally or peripherally, is well known, but functional diseases of the vagus may also bring about disturbances in the act of deglutition either by derangement of the vagus directly supplying the esophagus or by way of reflex. Reflex disturbances need not originate in the vagus; they may also originate in the sympathetic system. It is therefore reasonable to assume that cardiospasm is primarily an outcome of irritability of the vagus. The underlying factors bringing about such a state have been divided by Held and Gross,<sup>4</sup> into five groups.

In the first group are the patients whose vegetative nervous system is below par through inheritance. Almost throughout their lives they have some physical disturbance brought about by an unstable vagus or sympatheticus, and are also subject to cardiospasm. Although physically perfectly healthy, such people are found to have objective signs of vagotonia or sympathicotonia or the two mixed, and in the history we will hear that from childhood almost all organs supplied by the vegetative nervous system have at one time or another been subject to a functional disorder (enuresis nocturna, periodical vomiting, laryngospasm, urticaria, etc.).

To the second group belong the cases in which the vegetative nervous system becomes involved because of an inborn status asthenicus or status thymicolymphaticus. It is true that the status just named not rarely presents an inborn instability of the vegetative nervous system, but in a considerable number of cases we have found that the disturbance in the various organs brought on by

<sup>4</sup> Jour. Am. Med. Assn., June 22, 1916,

hyperirritability of the vagus and sympathicus is secondary. These individuals are not equal to the task of great responsibilities, either physically or mentally, and when overtaxed they need not necessarily acquire organic diseases, but they become subject to functional derangement of the vegetative nervous system. This may manifest itself in any of the organs supplied by the vegetative nervous system, and with equal frequency in the esophagus, causing cardiospasm. In this group belong the cases of gastroptosis, especially "long stomach" (langmagen), in which traction on the esophagus is the causative factor (Rovsing). Here also belong cases of cardiospasm resulting from sudden psychical trauma in individuals previously apparently healthy.

The third group contains the cases which show cardiospasm due to reflex irritation from other diseased organs (ulcus ventriculi, carcinoma of the fundus and lesser curvature, gall-stones, kidney-stones, diseases of the generative and genito-urinary organs, pancreatitis chronica or left-sided diaphragmatic pleurisy). Here, too, the underlying disturbed vegetative nervous system is a predisposing agent.

In the fourth group belong the cases of cardiospasm due to infections by toxic and metabolic agents (nicotin, lead, uremia, parasites, gout, chorea and lyssa).

In the final group belong the cases in which a local esophageal disease is the causative factor (fissure, erosions, scar-tissue formation and ulcus pepticum esophagi).

**Symptomatology.** It is important to know that the onset of cardiospasm is sudden and the first attacks may be of a short duration. Its transiency is best illustrated by two cases observed by us, one of a woman, who after a sudden shock by grief immediately developed cardiospasm which lasted several hours and recurred three weeks later. Another case is that of a man who presented clinical symptoms of cardiospasm which lasted three months. During fluoroscopic examination for half an hour the esophagus presented a characteristic sausage-shaped dilatation. Upon the administration of a Seidlitz powder, which was given merely as a suggestive measure, the spasm suddenly relaxed. These cases are cited to emphasize how frequently the affection is purely functional. In the majority of cases, however, once symptoms set in persistence is the rule. The severity of the symptoms varies, sometimes the patient can swallow solid food and no liquids, and at other times they can swallow liquids easier than solids. The severity of the symptoms depends greatly on the underlying causes. Often the patient will state that the first few morsels of food stop at the cardia and relief is experienced by taking more food; he even feels it going down into the stomach. When the condition persists, food stagnates in the esophagus, causing epigastric distress, substernal pressure, pain in the chest and belching and regurgitation of decomposed

food. There are often salivation and fetor *ex oris*. When extreme dilatation takes place the patient may have the false belief of feeling better, for he can partake of a larger meal. But if he takes a little more and reclines after it the food is regurgitated unchanged. Some patients vomit large quantities of food taken days before, simulating pyloric stenosis. This often leads to emaciation. In advanced cases the food is regurgitated in a state of fermentation and decomposition, showing the presence of lactic acid, butyric acid and sugar. In such cases due to these organic acids the patient has a continuous substernal burning. Pain as a symptom depends entirely upon whether the sensory nerves are co-affected or not. If so the pain is out of proportion to the disease and an attempt to swallow a little cold water causes severe pain in the region of the ensiform process, radiating to the soft palate, uvula, epiglottis, left side of the chest and sometimes both sides. Such pain is especially common if the spasm is due to a fissure at the cardia. A patient with cardiospasm observed by us was particularly troubled by pain as described above. Her blood showed a four-plus Wassermann and we hoped that antiluetic treatment might prove effective, which, however, was not the case. This made us doubt whether the existing lues was the underlying cause. Whereas the symptoms just described are typical of cardiospasm, very indefinite complaints such as feeling a fulness immediately after the smallest meal, belching and pressure in the epigastrium should lead us to examine carefully for a minor degree of cardiospasm. This is especially found in individuals of status asthenicus with a very long stomach in whom traction on the esophagus by the long stomach is supposed to cause spasm. To us it seems more plausible that the spasm is brought about by an undermined vegetative nervous system.

The physical examination should be directed not only toward establishing the disease, but also, if possible, to determine the cause; and therefore we should look for such clinical manifestations which indicate instability of the vegetative nervous system, *i. e.*, the vagotonic complex (Eppinger and Hess), such as dilatation of the pupils, slow pulse, slowing of the pulse when pressing on the eyeballs (Achner phenomenon), slowing of the pulse in bending forward, dry skin and pallor and spastic constipation. Not all symptoms must be present to complete the picture, and in reality some of the organs may show manifestations of sympathicotonia. Of course, it cannot be emphasized too strongly that the finding of symptoms of an unstable vegetative nervous system does not exclude organic disease. In fact it is to the credit of von Bergmann and his pupils, who demonstrated that such state predisposes to ulcer of the stomach and duodenum. It is surely of clinical importance to recognize the fact that in an organic disease like gall-stones or renal colic, if associated with cardiospasm, vagotonia plays quite a role as a predisposing causative factor.

**Sounding.** A soft stomach tube, not less than 10 mm. in width, should be used. In cases of spasm one has the sensation as if the tube were tightly held by the spastic esophagus. Sometimes sudden relaxation takes place and one feels the tube sliding down. The above-described sensation is more pronounced when a solid sound is introduced. The obstruction to the passage of the sound is not constant. Antispasmodics employed for a few days in the form of tincture belladonna, 10 minims, three times a day, or atropin,  $\frac{1}{100}$  grain, two or three times a day, or papaverin,  $\frac{1}{6}$  grain, three times a day for a few days, or benzyl-benzoate, 30 minims, three times a day, or making the patient drink some oil before the sound is introduced, may relieve the spasm.

**Esophagoscopy.** Most of the observers who use the esophagoscope with skill, such as Yankauer and Janeway, state that no definite information is obtained by this method. Both Rosenheim and Stark state that in certain cases hyperemia and in other cases ischemia were seen above the spasm, and also folds enclosing a narrow half-moon slit or even a pin-point opening above the spasm.



FIG. 1

**Roentgen-ray Diagnosis of Cardiospasm.** A most important radioscopic and roentgenographic sign is the visualized active peristalsis above the seat of the spasm. This is more marked in early and transient cases than in the advanced cases in which dilatation above the obstruction is very pronounced. The reason for that lies in the fact that the more the obstruction is due to spasm the more the



entire esophagus is in a state of hypertonus, and with its strong musculature tries to overcome the obstruction. In cases of obstruction at the cardia which result from idiopathic dilatation, where atony of the esophagus musculature is a primary factor, there is no peristalsis. Peristalsis of the esophagus is likewise absent in most of the cases of carcinoma at the cardia because of the associated loss of tone of the esophagus musculature. We differentiate two kinds of spasm: incomplete and complete. The former manifests itself fluoroscopically and roentgenographically as follows: The contrast substance is seen to hold at the point of obstruction and the esophagus above fills in an irregular spindle-shaped form exceeding its normal width two- or threefold. For a few moments nothing may be seen to pass through the obstruction. Repeated empty swallowing often overcomes the spasm. In the latter a uniform dilatation with visible contraction is seen above the obstruction. Through the obstructed area nothing may pass or a very thin streak of the contrast meal. If the condition persists for a very long time, dilatation may be so advanced as to permit the esophagus to hold from 200 to 300 cc of fluid. We can then see fluid in the dilated esophagus even without contrast substance. The esophagus looks sausage-shaped (Fig. 1), but shows peristalsis. The presence of peristalsis serves to differentiate cardiospasm from idiopathic dilatation or dilatation due to obstruction by cancer.

**Rumination (Incomplete Cardiospasm).** It seems of interest to us to record in this connection a case of rumination we had occasion to observe. While the patient swallowed the contrast meal which after a few morsels was seen to pass into the stomach with ease, the lower half of the esophagus would suddenly dilate and the patient would feel the food come back into the mouth. The patient would rechew it and swallow it again, then the food would suddenly drop into the stomach. This fluoroscopic study was an excellent demonstration of Meltzer's physiological studies as to the act of deglutition, *i. e.*, that the closure at the mouth of the esophagus during swallowing brings about the opening of the cardia (Figs. 2 and 3). Fig. 2 was taken immediately after the contrast substance was swallowed and Fig. 3 was taken one minute after the patient was asked to swallow empty. While fluoroscoping the patient during the act of deglutition we asked him to give a signal the instant he felt the food pass back into the mouth. The signal corresponded exactly to the time when the spasm in the cardia set in. This observation gave us a hint to advise the patient, instead of ruminating, to reswallow as soon as he felt the food back in the mouth or at the first sensation of distress in the epigastrium. Since then the patient reported repeatedly considerable improvement but not cured. Another illustration of how disturbance in the region of the mouth of the esophagus produces reflexly cardiospasm is demonstrated by a case of Zenker's diverticulum as shown in Figs.



FIG. 2

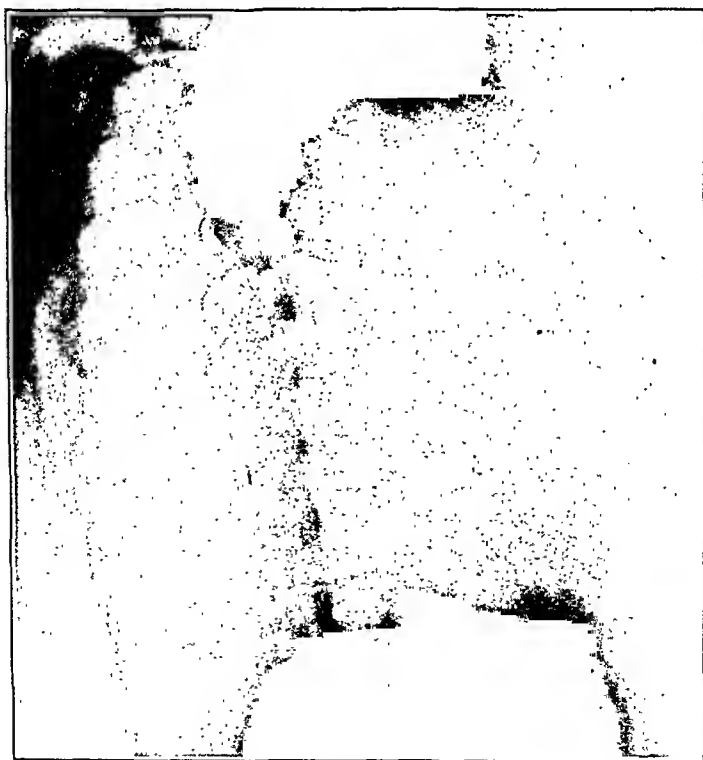


FIG. 3

4 and 5. (Fig. 4 shows the diverticulum and Fig. 5 the spasm.)  
Another case worth mentioning in which cardiospasm was caused



FIG 4



FIG. 5

by pressure in the upper part of the esophagus was due to an aortic aneurysm. It is interesting that these patients in whom the cardiospasm is brought about by disturbance in the upper part of the

esophagus, either as a result of disturbance of innervation (the case of rumination quoted above or anatomical defect, as in the case of Zenker's diverticulum, or if due to pressure from without, as in the case of aortic aneurysm) complain that the food stops in the throat or in the upper part of the esophagus.

**Regional Spasm of the Stomach.** Approaching the stomach proper the most frequent seat of regional spasm is that of the pylorus, so-called pylorospasm. Pylorospasm is a condition in which a part or the entire pylorus is in a spastic state for a shorter or longer duration. When a spasm persists for a long time it may even lead to hypertrophy and marked thickening of the pylorus with a resulting palpable mass simulating a tumor.

**ETIOLOGY.** Pylorospasm may be caused by intra- and extra-gastric disease (intrinsic and extrinsic—Carman). The intra-gastric cause is by far the less frequent, and if present is mostly the outcome of a prepyloric ulcer less frequently due to ulcer on the lesser curvature of the stomach and still less frequently in duodenal ulcer. We have seen it occur in gastro-enterostomized patients. Like Carman and Miller we saw it occasionally in carcinoma of the stomach.

The extragastric causes for spasm are numerous. According to our experience gall-bladder disease heads the list. Holzknecht and Luger were the first to call attention to the frequency of pylorospasm in gall-bladder disease, and they pointed out that the existence of a solitary stone in the gall-bladder is more prone to give rise to such spasms than multiple stones. Their observations were since then confirmed by Carman, Case and others. Our experience as demonstrated by Fig. 6 fully confirms their views. Other causes are chronic pancreatitis, chronic appendicitis, renal calculi, chronic lead-poisoning, morphine-poisoning, tabes dorsalis and chronic interstitial nephritis, particularly during the stages of suburemia and uremia.

**SYMPTOMS.** These, of course, vary, depending on the underlying cause. Where an intragastric cause like ulcer or cancer is responsible the well-known symptoms are present, which need no discussion. We consider it of sufficient importance to dwell more or less fully on the discussion of pylorospasm produced by gall-bladder disease, particularly gall-stones. Such individuals, independent of gall-stone colic, or even in the absence of any acute attack, have a long and persistent row of vague gastric symptoms. They complain almost continually of fulness in the upper quadrant of the abdomen. Just as soon as they begin to eat they feel that they have to stop because of pressure in the epigastric region, which is often relieved by spontaneous or forced belching. They often complain of pain of varying severity relieved by the application of heat. Such slight attacks generally occur during eating. Mental and physical exertions have a more deleterious effect than dietetic errors. The

tendency for these symptoms is to persist and eventually to lead to emaciation and pallor, and in extreme cases almost resembling carcinoma of the stomach. These symptoms, vague as they are, in the absence of definite physical findings, are often attributed to neurosis, and, in a sense, they are neurotic and functional in nature. These patients in the majority of cases have an unbalanced autonomic nervous system. By physical examination alone, no matter how painstaking it may be, it is very difficult to establish a diagnosis. Even the best palpation, including the Housman deep-sliding method of the pylorus, will seldom determine the existence of a spastic pylorus. In the pre-roentgen-ray era experts on palpation claimed to have succeeded in palpating a spastic pylorus.



FIG. 6

Experts, however, are the exception. The roentgen-ray, on the other hand, makes us visualize spasm with ease and offers an explanation for the symptoms.

The roentgen-ray findings are as follows: Fluoroscopically the food is seen to stop at the antrum, and sometimes even for several minutes no food at all is seen to pass, and what enters the pylorus appears in the form of a narrow canal or pivot-shaped. Palpation does not change the contour of the pylorus. The roentgen-ray plate (Fig. 7) shows the above-described phenomenon. The stomach proximal to the contracted pylorus shows dilatation and active peristalsis. It was already stated above that the clinical and roentgen-ray manifestations are such that to distinguish between these and carcinoma becomes very difficult. We may state that we, like others, had cases of persistent pylorospasm with anacidity.

These we submitted to operation with a doubtful diagnosis, but inclined to carcinoma. In 2 cases the pylorus was so hard and thick that the surgeon had to open the pylorus to convince himself that there was no tumor within. One of the cases was operated by Dr. Richard Lewisohn and the other by Dr. A. A. Berg. In cases in which the hypertrophied pylorus gives rise to a palpable mass and the contrast meal fails to fill the pylorus the differential diagnosis between spasm and cancer is almost impossible.

Regional spasm may occur in the fornix or tube of the stomach. In these cases it is brought about by pressure from without. We observed a patient in whom a large spleen made the upper part of the stomach from airbag to midpart of the tube appear like a narrow rigid canal with no peristalsis and a very small and deformed

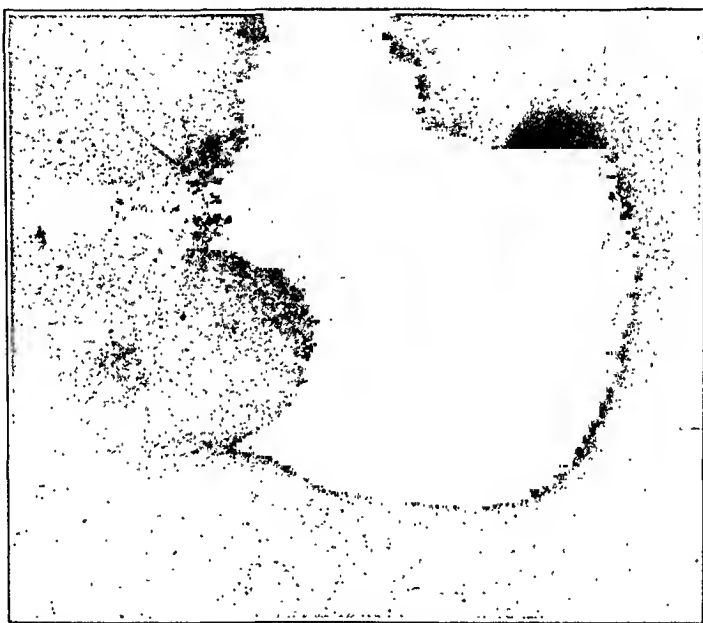


FIG. 7

air-bag. The palpable mass of the left side, which was the enlarged spleen, awakened the suspicion that the tumor might have been due to a malignant disease of the stomach. Inflation of the colon with air made the outline of the spleen to the palpating hand more definite. A more extensive spasm of the stomach, taking in the tube and pylorus and making the cardiac end appear funnel-shaped, was seen by us in a woman with a large fibroid tumor of the uterus. A similar spasm of the fornix and part of the tube was seen by us in a case which at the laparotomy performed by Dr. William Spickers disclosed tuberculous peritonitis with tubercles scattered over the serosa of the stomach (Fig. 8).

Regional spasm of the tube or pars media, with dilatation of the cardiac end and the pylorus, is sometimes encountered. It is usually

of extragastric origin and only the clinical history can establish the cause.

A frequent seat of regional spasm is encountered in the stomach just below the incisura cardiaca. We do not refer to the standing



FIG. 8



FIG. 9

contraction or the incisura on the greater curvature. This is to be discussed below. What we have reference to here is, as shown in Fig. 9, that the contrast substance is held at the point mentioned above. The fornix is seen dilated and sometimes from five to ten minutes either no food is seen to come down or only a thin streak

of contrast substance along the lesser curvature. In the former case the fornix presents a pear-shaped or triangular appearance (Fig. 10); in the latter case the narrowing below the dilatation bears resemblance to a cardiospasm with the dilated esophagus above it. We have therefore conceived the idea that the spasm is not only local, but that it involves the greater part of the tube. We were led to this observation accidentally, viz., through a patient who complained of severe choking sensation, pressure and fulness in the epigastrium after meals. The symptoms were at times so annoying that he would have to stop, when on the street, at any physician's office for the purpose of obtaining relief, for he feared lest he might choke. Nose and throat examination by specialists was pronounced

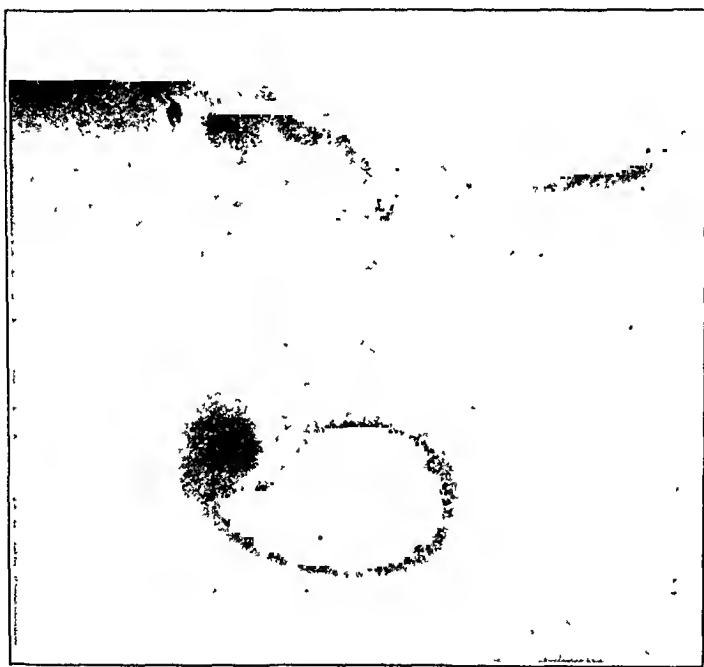


FIG. 10

negative. We studied his esophagus fluoroscopically with a contrast emulsion, as advocated by I. S. Hirsch, in order to exclude obstruction or a diverticulum of the esophagus. The esophagus was found to be normal, but as the emulsion entered the fornix it filled out that part and no particle of the contrast substance was seen to enter the tube. Massage of the fornix could not press the food down. Only after a few minutes a thin streak was seen to dribble down along the lesser curvature. It appeared to us as if we were dealing with an organic hourglass contraction. We then gave him the ordinary barium-buttermilk meal and the stomach filled completely. We had the patient return two days later after the administration of belladonna (according to the method of Carman) and repeated



the examination as before, and observed the same phenomena. A few days after the second examination we examined him again with the ordinary barium-buttermilk meal, when this phenomenon was entirely absent. When we then questioned the patient a little more in detail about his gastric symptoms most of his complaints, clinically, suggested gastric ulcer. The chemical analysis of the stomach contents showed marked hyperacidity. We placed the patient on a Sippy treatment, with gratifying results.

We were at once impressed by the thought whether the spasm below the fornix, just at the junction of the fornix with the tube, may not give rise to symptoms of spasm in the upper part of the esophagus similar to cardiospasm. We also reasoned that where there is an irritated area at a certain point in the stomach a meal that would tax that part of the stomach more than the buttermilk meal may demonstrate the functional disturbance brought about by such irritation.

We have since then adopted the procedure to start all our gastrointestinal roentgen-ray examinations with a few tablespoonfuls of the barium emulsion. We may state now definitely that normally this emulsion is seen to pass down the lesser curvature without stopping in the fornix. This emulsion fills out the fornix better than the barium-buttermilk mixture, and therefore outlines it when it would otherwise not be seen. Thus far our observations of such spasms have led us to believe that the cause for the same is intrinsic, and in the majority of cases is most likely due to an ulcer on the lesser curvature at the point where the ulcer exists. The spasm seems to us to be a protective phenomenon, analogous to the spasm in the sphincter pylori in cases of pyloric ulcer.

Another point of very frequent regional spasm is that of the sphincter pylori. This condition is often brought about reflexly by chronic appendicitis, colic mucosa and is also often functional. It has great significance in erosions and ulcer in the region of the sphincter pylori. Such erosions may give rise to periodical gastralgia, terminating in vomiting large quantities of fluid, but rarely solid food. Vomiting gives great relief; morphine, on the other hand, may make the condition worse. If the condition lasts a long time, dilatation and hypertrophy of the pylorus become so marked as to give rise to a palpable tumor. Schnitzler<sup>5</sup> reported a case in which a tumor the size of an orange was felt in the epigastrium. That patient was operated. At first the surgeon did not find any evidence of a tumor, but while palpating the pylorus the tumor reappeared. A similar case was observed by us. Schnitzler considers an erosion in the sphincter pylori analogous to an erosion in the sphincter ani, and advises pyloroplasty in such cases.

The fluoroscopic and roentgenographic appearance in such cases is most striking, as shown in Fig. 11. The pylorus appears as if

<sup>5</sup> Wien. med. Wchnschr., 1891.

suddenly cut off and is immensely dilated. Forcing the food out while fluoroscopic we see only a narrow stream of contrast substance which fills the first portion of the duodenum very thinly, giving it the appearance of a goose feather. Sometimes we may watch for several minutes without seeing any food going through the pylorus. If we fluoroscope and make plates of such cases an hour or two after the ingestion of the contrast meal very little is seen to have left the stomach. If the spasm is of extragastric origin it is usually very transient and there is only a very moderate delay in the emptying of the stomach, and, as a rule, no six-hour residue is present. If there be a large six-hour residue in such cases we usually find the rest of the contrast substance in the terminal ileum, which is considerably dilated. The cecum, as a rule, contains very



FIG. 11

little or no contrast substance at all. This seems to us to indicate the existence of a spasm in the sphincter of the ileocecal valve, and that is most likely the primary cause of the spasm in the sphincter pylori. The delay in the emptying of the stomach may not depend entirely on the persistence of the spasm in the sphincter pylori, but to a great extent upon the fact that the small intestines are filled, and therefore the so-called intestinal hunger (Pawlow) is not present.

When the spasm of the sphincter pylori is due to a local erosion the six-hour residue is large, the terminal ileum containing little contrast substance, or may be entirely empty, and the distribution through the colon may not be normal. The reason that the small intestine contains so little contrast substance, although the stomach

contains much, is explained by the fact that the food is so thoroughly liquefied in the stomach that it runs through the small intestines rapidly.

**Incisura.** The incisura or spastic hourglass has been made accessible of recognition by means of the roentgen-ray. It appears mostly on the greater curvature, a little below the incisura cardiaca. It may, however, appear in any other part of the greater curvature of the stomach. It may be transient or persistent. There is, usually, one incisura, but two or three may be present. The depth and width of the incisuræ vary from that of a small nick to a deep indentation reaching the lesser curvature and giving the stomach a bilocular appearance (Fig. 12). Where there are two or three incisuræ the



FIG. 12

stomach appears as if it were divided into several compartments. These incisuræ may be of extra- or intragastric origin. Such incisuræ are met with occasionally in cases of chronic appendicitis and gall-stones. Very rarely they appear spontaneously in such cases during fluoroscopic examination, but more commonly, as pointed out by both Case and Carman in this country and Borsany and Hurst abroad, such incisuræ are brought about when pressure is exerted over the diseased organ (appendix, gall-bladder and duodenum) while fluoroscoping. Even under such circumstances it is not a common occurrence. It has been our experience that when pressure on the diseased appendix or gall-bladder brings about such indentation it is very transient and lasts only as long as the pressure is continued. More commonly it is seen in neuropathic individuals,

especially when vagotonia is predominant. Also, pressure from without, such as a tumor in the left hypochondrium, a large spleen or even gas in the splenic flexure, may produce such spasm. The most important intragastric cause for spasm is an ulcer on the lesser curvature of the stomach opposite the incisura (Fig. 13). The spastic incisura, whether of extra- or intragastric origin, may be transient and disappear spontaneously while fluoroscoping or may persist during one examination and be present at the next examination. Deep and wide incisuræ, situated opposite an indurated or penetrated ulcer on the lesser curvature, are usually persistent and only disappear under deep narcosis. That is why the surgeon in the early days of roentgen-ray diagnosis contradicted the roentgen-ray

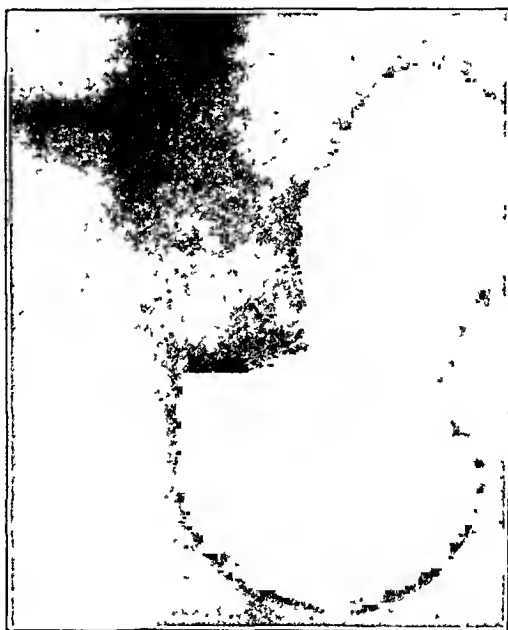


FIG. 13

findings of an hourglass. The differential diagnosis between spastic incisuræ of extragastric origin and that due to ulcer on the lesser curvature of the stomach is made by the administration of antispasmodics like atropin or tincture of belladonna, according to the method of Carman, or papaverin or atropapaverin, as advocated by Holzkecht and Skolitzer.<sup>6</sup> The disappearance of the incisuræ after antispasmodics, according to our opinion, does not exclude an ulcer on the lesser curvature. The persistence of the incisuræ, on the other hand, especially if a niche is seen on the lesser curvature, establishes the diagnosis of ulcer with absolute certainty.

A rare type of incisura occurs on the lesser curvature just below the air-bag, indicating the seat of an ulcer. A case with such incis-

<sup>6</sup> Wien. klin. Wchnschr., 1913, No. 26.

ura observed by us showed at operation no ulcer but a large solitary stone in the gall-bladder. Another rare form of incisura is mentioned by Faulhaber, from whose monograph Fig. 14 is taken. In this type the cardia is to the left and is accompanied by a narrow isthmus to the rest of the stomach which lies to the right. Primarily, Faulhaber correctly interpreted this as being due to an ulcer on the lesser curvature or to adhesions of the posterior wall of the stomach to the pancreas. Recently a number of publications appeared in foreign literature, notably among which are those of Rieder, Zehbe<sup>7</sup> and E. Schlesinger.<sup>8</sup> Rieder named this form of a stomach a cascade or waterfall stomach (Fig. 14). This form of a stomach presents a standing contraction or incisura on the greater

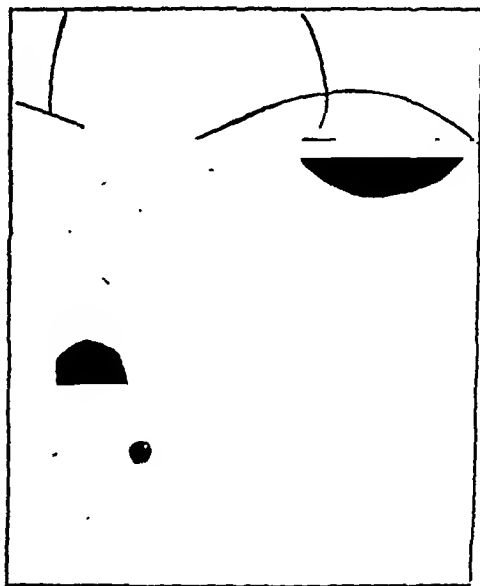


FIG. 14.

curvature just below the cardia, but instead of the corpus and pylorus running in the vertical axis the corpus and pylorus in the cascade stomach adopt the sandal or bull-horn shape. It seems justifiable to assume that such a stomach presents evidence of regional and partial gastropasm combined. The regional spasm is demonstrated by the incisura and the partial by the narrow transversely situated tube and pylorus. That this condition is purely spastic is evidenced by the fact that it is not persistent and that it frequently disappears after the use of antispasmodics. Both intra- and extragastric disease play a role in the etiology of this condition.

<sup>7</sup> Fortsch. auf dem Grenz., Roentgen Strahlen, vol. xxv, p. 107.

<sup>8</sup> Ibid., vol. xxvii, p. 261.

It is a striking fact, which was observed by E. Schlesinger and confirmed by others, that duodenal ulcer frequently brings about such spasm. Fig. 15 shows a duodenal ulcer in a cascade stomach observed by us. Such condition can also be brought about by gas distention of the descending colon, a large spleen or tumors in the left hyperchondrium. In such a stomach the cardia or fornix is dilated, the air-bag is broad and presses against the left dome of the diaphragm with resulting clinical symptoms brought about from such pressure. This may also explain the frequent occurrence of left-sided pain in the duodenal ulcer. The organic hourglass of the



FIG. 15.

stomach due to ulcer, cancer and syphilis of the stomach will not be discussed here, as it does not belong to our subject. Before leaving the subject of incisuræ it seems in place to call attention to the fact that the phenomenon was much more frequently seen in the early days of gastro-intestinal roentgen-ray studies than now. This question has confronted us, and we thought that the reason for it may be in the difference of the consistency of the contrast meal. In the early days when a semisolid carbohydrate meal of Rieder was used the quality and consistency of the meal was of a nature to tax the peristole in the fornix and upper part of the tube unless the stomach was very markedly hypotonic or atonic. A carbo-

hydrate meal remains longer in the fornix because salivary digestion continues there for a few minutes. The spastic incisura on the greater curvature has been considered as a protective phenomenon to prevent the food from irritating the ulcer-bearing area.<sup>9</sup> When a light fluid meal like the barium-buttermilk meal is given the meal is not sufficiently irritating to call upon such protective phenomena. A further proof that the lack of the filling of the fornix is responsible for the rarity of the incisura is furnished by the fact that when the fornix is made to fill by postural changes, such as having the patient lie on his back and obliquely (Levy-Dorn), an incisura may be brought out when it would not otherwise be seen. This cannot be due to local pressure from without because that position serves to evade pressure. We have therefore adopted the procedure to study all our cases in the Levy-Dorn position, with the barium emulsion as described above. If after such examination a conclusion is not reached the patient should be reexamined with a Rieder meal. The reason we do not start the Rieder meal at first is because the fluid meal is better adapted for the study of the first portion of the duodenum and the appendix.

**Total Gastropasm.** Total gastropasm is the rarest of all forms of spasm and is in most cases of extragastric origin. Cases reported in the literature were due to chronic lead-poisoning, tabes dorsalis and morphinism. A case was seen by us in which the stomach looked like a narrow tube without any peristalsis and a gaping pylorus, and which we diagnosed as scirrhus cancer. This patient was operated by Dr. T. A. Dingman and no lesion was found in the stomach, but the appendix showed evidence of chronic inflammation. A case is mentioned in the literature which was due to gallstone disease. Carman reported a case of gastropasm produced by a small cancer on the lesser curvature of the stomach. Gastropasm is characterized by an extreme hypertonus. The stomach is considerably diminished in size. It is situated very high in the abdomen, most of it to the left of the median line. The air-bag is small, peristalsis is almost absent and the food is seen to pass continuously into the small intestine. It resembles almost entirely a scirrhus cancer. The resemblance of all forms of gastropasm to filling defects due to cancer is so striking that rightfully does Carman make the statement that not only is the novice in danger of mistaking it for cancer, but the expert as well.

<sup>9</sup> Held and Gross: *AM. JOUR. MED. SC.*, May, 1918.

## THE BEST TECHNIC FOR GASTROENTEROSTOMY AS DETERMINED BY FUNCTIONAL RESULTS.

By ABRAHAM O. WILENSKY, M.D.

NEW YORK.

(From the Surgical Division of Mount Sinai Hospital, Service of Dr. A. A. Berg.)

For a number of years the operation of gastroenterostomy has been gradually losing in favor, and at the present time dissatisfaction with this surgical procedure is approaching an extreme point. It has therefore seemed to be of value to summarize observations made on patients subjected to this operation with the object of demonstrating the accompanying and resulting phenomena; these seem to explain amply the reasons for this dissatisfaction. And inasmuch as the making of a gastroenteric anastomosis is on occasion a necessity, the observations have further value in enabling a selection of the best type of technic for this purpose. It seemed best to utilize only the clinical notes and observations of patients actually afflicted with ulcerative conditions; animal work did not seem appropriate, since none of the ordinary laboratory animals are naturally susceptible to this disease.

The methods employed in making these studies depends upon the estimations of the functional capacity of the stomach and were fully described on a previous occasion. Inasmuch as gastroenterostomy is most frequently made for chronic ulcerations of the stomach or duodenum, none other than these ulcer cases, except for the control cases, are included in the report. The patients upon whom these studies were made were not selected in any way and the studies were made *seriatim* as the patients were consecutively admitted and discharged.

The necessary control observations were made by selecting a number of patients in whom at exploratory operations it was definitely established that no pathologic lesion existed in the stomach or duodenum. The observations made in these cases before and after operation showed close similarities. The facts of these observations are summarized in Table I and Fig. 1. In detail these are:



TABLE 1.

## MOTOR FUNCTION.

Case.	Roentgen-ray.		
	Tone.	Peristalsis.	Empty in
1	Good	Active	4 hours.
3	Good	Active	4 hours.
4	Good	Active	6 hours.
2	Fair	Fair	6 hours.
6	Good	Active	6 hours.
7	Good	Active	6 hours.

## CHEMISM.

Case.	Fasting contents; residue in cc.	Ewald test-breakfast.			Riegel test-meal; residue in cc.
		Residue in cc.	Free acid.	Total acid	
1	0	40	35	65	0
3	0	100	50	75	0
4	0	60	..	..	0
2	0	75	35	75	0
6	0	50	60	80	0
7	0	35	30	60	0

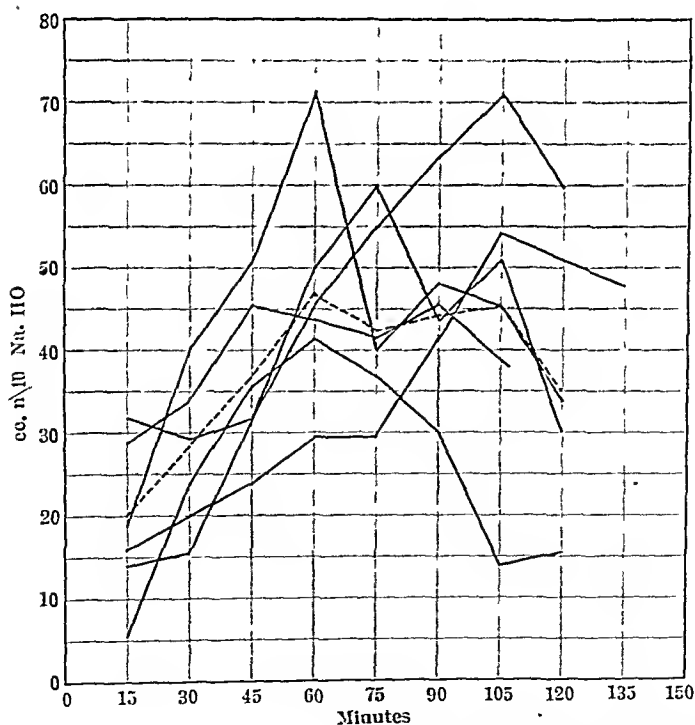


FIG. 1.—Fractional test meal. Specimens extracted until the stomach is empty. Estimations in terms of cubic centimeters of decinormal sodium hydrate solution. The dotted line represents the average of all the curves in the figure. These facts apply to Figs. 2, 3 and 4 also.

1. There is no fasting contents in the stomach or, at most, it consists of a few cubic centimeters. The latter is mostly mucus, more rarely a thin watery fluid, and very rarely is bile-tinged. It usually contains no or very little free hydrochloric acid and a low total acidity. Frequently there is no acid content.

2. After an oatmeal gruel test meal hydrochloric acid is secreted rapidly and the total concentration rises and reaches its maximum approximately sixty minutes after ingestion. Thereafter the total concentration tends to fall and approach the level from which it began.

3. The secretion of digestive enzymes is constant and the latter can always be demonstrated in abundance.

4. Depending on the character and quantity of food the stomach is emptied after a certain time and afterward the stomach contents resemble the original fasting contents. With carbohydrate meals the average emptying time is from two to three hours; with protein meals, six hours or more.

5. The motor activity of the stomach wall is normal. The roentgen-ray demonstrates that peristalsis is active and efficient; with the barium zoölak contrast meal the stomach is seen to be empty within six hours.

These are the salient characteristics of normal stomachs.

The biologic history of chronic ulcer of the stomach or duodenum includes definite manifestations of disturbances in the normal physiologic activities. In previous studies these were all severally considered. It was possible to demonstrate that functional disturbances were not always present to any considerable degree and that there was no elicitable relationship between the situation of the lesion, its size or structural characteristics, or of any anatomic complication, and the character and intensity of the physiologic changes and of the subjective symptomatology. Without going into any detailed description of these relative factors the progression of the illness is, in the large majority of cases, accompanied by a progressive increase in the functional disturbance; this is especially marked in the motor aspects.

There are several ways of making a gastroenteric anastomosis and the procedure may be added to by creating an artificial blocking to the passage of the stomach contents through its normal outlet (unilateral pyloric exclusion). The operation usually done follows the method of von Hacker, and the anastomosis is made either by suture or by the Murphy button, depending on the ease with which either could be done or on the exigencies of the individual case; preference has always been given to the suture method. With the suture method the stoma is made large enough to easily admit two fingers, and is given a vertical application to the posterior wall of the stomach, as near to the pyloric end and the greater curvature as can easily be reached through an opening in the

mesocolon made to the left of the middle colic artery. The afferent loop is as short as possible. The efferent loop is most commonly turned to the right and passes downward and to the right in the general direction of the right iliac fossa. In exceptional cases the efferent loop is allowed to follow its natural inclination; it then passes downward and to the left in the general direction of the left iliac fossa. The pylorus is always excluded by the string method unless sufficient stenosis of its lumen already preëxists.

The operation of gastroenterostomy causes a distortion of the normal structure and contour of the stomach and of its anatomic relationships. This probably secondarily causes changes in the normal nervous mechanism controlling the normal gastric functions. Even when all the wounds are surgically healed in a manner most acceptable in the present state of our knowledge certain changes in the physiology are therefore inevitable because of this new anatomy. When superimposed upon the previously existing anteoperative deviations from the normal physiologic function the effects of the operation may be one of two: In many the immediate influence is of a beneficial nature and is amply demonstrated both by the subjective symptomatology and by the objective functional capacity of the stomach as determined by appropriate laboratory tests. In some the resultant immediate effect shows no improvement in the functions of the stomach from its preoperative status. In a very few an exaggeration of the latter status appears usually approximately equal to the old disturbances plus those due to the changed anatomy. The possible combinations probably furnish a very fertile field for the presence of postoperative symptoms.

This conception furnishes a ready explanation for the good results which usually follow a gastroenterostomy done for cicatricial pyloric stenosis; here an anatomic abnormality existing for a long period of time has caused accompanying changes in the normal physiologic mechanism, the progression of which holds an almost mathematic ratio with the degree and duration of the stenosis. After a certain time the disability reaches the point where the exhibited compensatory efforts of the stomach eagerly await a change in structure sufficient and competent to enable the organism to adjust itself satisfactorily to the new conditions. The gastroenterostomy accomplishes this in the most desirable way, and the postoperative compensation is therefore made with no or very little symptomatic disturbance.

The changes which follow gastroenterostomy have a wide latitude and can be considered from various viewpoints. The functional results were preliminarily studied without regard to the type of technic employed in the operation or to the secondary changes which had followed the essential ulcer pathology. Several tables

are appended in which this knowledge is summarized<sup>1</sup> (Fig. 2, 3 and 4).

Table II consists of cases in which at the time of the examination there were no subjective symptoms of any kind.

TABLE II.  
MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
4	Closed	Patient	Good	4 hours.
10	Patient	Patient	Fair	6 hours.
16	?	Patient	Good	6 hours.
19	?	Patient	Good	4 hours.
6	Patient	Patient	Good	?
22	-			

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
4	30	0	18	225	24	54	?		
10	30	4	10	70	50	86	0		
16	5	0	0	20	0	56	0		
19	10	0	0	60	0	14	?		
6	70	0	10	80	0	12	?		
22	25	10	22	75	16	46	?		

Table III includes cases in which an exhibition of symptoms indicated an incomplete readjustment to the new conditions either because of insufficient compensatory effort or because of the preoperative extraordinary degree of derangement. The studies seemed sufficient to make the assumption probable that no anatomic lesion was present. The degree of individual disturbance as indicated by the symptomatology showed wide variations.

<sup>1</sup> These tables should not be interpreted as indicating in any way the number or percentage relationships of the cases cured or not cured.

TABLE III.  
MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stomn.	Peristalsis.	Empty in.
2	Patent	Closed	Active	6 hours.
32	Patent	Patent	Active	6 hours.
5	Patent	Closed	Very active	?
12	Patent	Patent	Very active	2 in 1 hour.
11	Patent	Not efficient	Very active	6 hours.
9	Patent	Not efficient	Fair	6+ hours.

## CHEMISM.

Case.	Fasting contents.			Ewald Test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
2	25	10	22	220	38	63			
32	25	12	30	60	16	65	40	14	30
5	90	46	48	300	44	64			
12	16	10	25	160	11	45			
11	65	21	41	125	36	68			
9	1	0	0	350	14	51	100	0	55

Table IV includes cases in which at secondary exploratory operations it was definitely proved that the symptomatology was directly due to anatomic lesions. In these cases also the degree of disturbance as indicated by the subjective symptomatology showed wide variations.

These tables demonstrate rather conclusively that the operation of gastroenterostomy, even when the postoperative course is seemingly ideal from every standpoint, is followed by certain changes in the physiologic mechanism of the stomach. The changes involve both the motor and chemical functions of the stomach, and it is not easy to distinguish the relative positions of either. It seems, however, from all that one knows that the motor function is most important for the proper working of the stomach; and it is more than probable that in many, if not in all, the chemical changes are secondary to the motor. The direction which the latter assume is toward a progressive retardation of the passage of the stomach contents onward in the alimentary canal.

With the appearance of postoperative symptoms of one kind or another a study of the individual functions indicates that the degree of physiologic derangement becomes progressively greater as the attempted readjustment is retarded or disturbed because of functional causes and reaches a maximum when the compensation is interfered with by the presence of mechanical obstacles to the proper motor functioning of the stomach (narrowing of the

stoma in the presence of a spontaneous or operatively produced pyloric obstruction).

TABLE IV.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
13	Patent	Not seen	Violent	6+ hours.
3				
14	Patent	Not seen	Violent	6+ hours.
18	Patent	Patent inefficient	Hyperperistalsis	?
24	Patent	Inefficient	Hyperperistalsis	6+ hours.
27	Patent	Patent	Active	6 hours.

## CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
13	44	8	21	190	30	64			
				450	30	50			
3	60	12	46	90	24	66	27	0	73
14	60	27	54	210	34	52			
18	50	27	41	200	39	53			
24	10	0	0	600	33	50	30	0	18
27	..	..	..	20	17	35	50	46	86

It seems to be true that in many of the cases in which these deviations from the normal take place the change becomes permanent. In a series of cases which were studied for periods up to four years after operation it could be demonstrated that while the chemical function remained practically in the same condition in which it was prior to operation the delay in emptying time, as demonstrated by test meals, persisted and grew larger as time went on. This is well shown in Table V. The roentgen-ray is not very reliable for determining this point, inasmuch as frequently the passage of a stomach tube is productive of stomach contents when no contrast meal is visible either fluoroscopically or on a photographic plate.<sup>2</sup>

TABLE V.

## EWALD TEST-BREAKFAST.

	Residue in cc.	Free acid.	Total acid.
Before operation . . . . .	74	47	72
1 to 4 months postoperative . .	127	27	61
4 to 12 months postoperative . .	148	27	54
1 to 4 years postoperative . . .	190	32	60

<sup>2</sup> I am indebted to Dr. Held for this observation.

The subject under discussion might also be viewed with reference to the type of technic employed in the operation of gastroenterostomy. As indicated in the beginning of this communication this would enable a selection of that method of operating for routine purposes which would be followed most often by a minimum change from the normal standards; it was hoped that in that way the temporary or permanent disagreeable sequelæ, especially those in the period of readjustment after operation, might be obviated altogether or minimized as far as possible.

In most clinics the principal techniques employed in gastroenterostomy include (a) posterior gastroenterostomy by suture or (b) by the Murphy button; (c) either of these in combination with a pyloric exclusion. The observations hereinafter summarized have to do with these three types of technic. In those cases in which ulcers were found and operations were done upon the stomach the patients were allowed to recuperate completely. Then the functional capacity of the stomach was again determined in the manner previously alluded to.

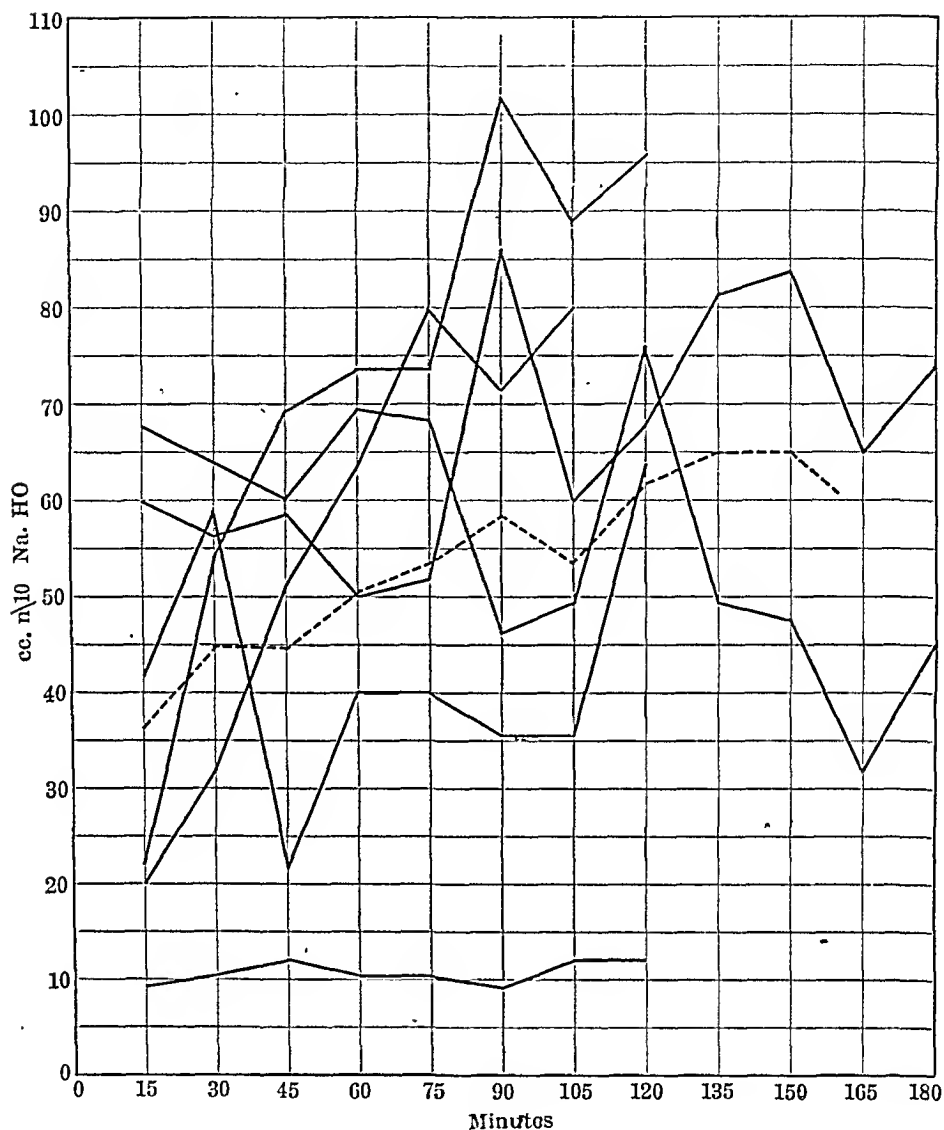
In the suture gastroenterostomy cases in which no pyloric exclusion was practised the obtainable facts are gathered in Table VI and Fig. 2.

TABLE VI.  
MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
1	Open	Patent	Active	9 hours.
12	Open	Patent	?	2 in 1 hour.
14	Open	Patent	Violent	6 hours.
25	Open	Patent	Very active	6½ hours.
46	Open	Patent	Good	Over 6 hours.
64	Open	Patent	Good	Over 6½ hours.

CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
1	60	0	14	100	4	8			
12	20	16	25	160	11	45			
14	80	27	54	210	34	52			
25	25	18	31	70	32	94	25	36	62
46	35	42	60	40	30	50	0		
64	5	0	0	110	11	42	5	0	0



In the second group of cases a pyloric exclusion by the string method was done in addition to the suture gastroenterostomy. The elicitable facts are summarized in Table VII and Fig. 3. A comparison of the observations in this group with those in the previous group enabled an evaluation of the effect of the string method of pyloric exclusion.



TABLE VII.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
4	Closed	Patent efficient	Good	4 hours.
2	Open	Not patent	Moderate	6 hours.
17	Closed	Patent	Fair	6½ hours.
39	Open +	Patent ++	Good	6½ hours.
53	Closed	Patent	Fair	6½ hours.
66	Closed	Patent	Fair	6 hours.

## CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
4	27	13	30	350	20	45	60	0	27
2	26	10	22	200	38	63	58	0	16
17	75	22	40	150	50	71	70	58	83
39	30	60	80	110	68	96	40	14	50
53	0	..	..	265	30	48	0		
66	0	..	..	100	15	60	50	38	47

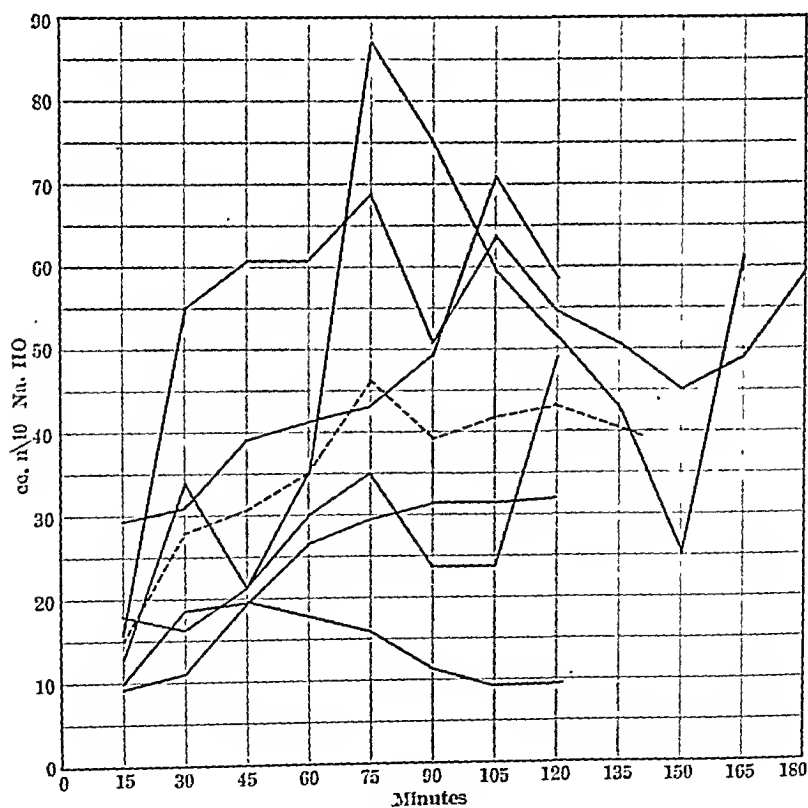


FIG. 3

In the third group the gastroenterostomy had been made with the aid of a Murphy button and a pyloric exclusion had been made with the technic described in the previous paragraph. The facts are grouped in Table VIII and Fig. 4. A comparison between the second and third groups enabled a judgment as to whether the suture or button operation was superior.

TABLE VIII.  
MOTOR FUNCTION.

Case.	Roentgen-ray.			
	Pylorus.	Stoma.	Peristalsis.	Empty in.
10	Open ++	Patent +	Good	6 hours.
16	?	Patent	Good	6 hours.
22	Closed	Patent	Active	6 hours.
48	Open	Not seen	Fair	
55	Open	Not seen	Fair	6 hours.
50	Closed	Patent	Active	6 hours.

#### CHEMISM.

Case.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
10	30	4	10	70	50	86	0		
16	5	(mucus)	..	100	0	50	0		
22	16	0	?	70	4	50	15	34	52
48	0	..	..	180	66	88	35	34	52
55	15	8	24	150	38	76	50	68	90
50	0	..	..	30	28	52	90	56	74

The average findings in the three groups studied are compared in Table IX. In a general way these observations correspond with those noted in the earlier tables; there are larger residues after the various test meals, and the general run of acid concentrations does not show much deviation. In the individual groups it is to be noted in most of the cases that the suture operations yield a larger residue after the test meals when an exclusion has been simultaneously practised. In contradistinction to these two groups of suture operations the button operations seem to yield residues which more nearly approach the normal. The smallest fasting stomach contents is obtained after the button operation. The average functional result after a suture operation without an exclusion seems to equal that of a button operation with an exclusion.

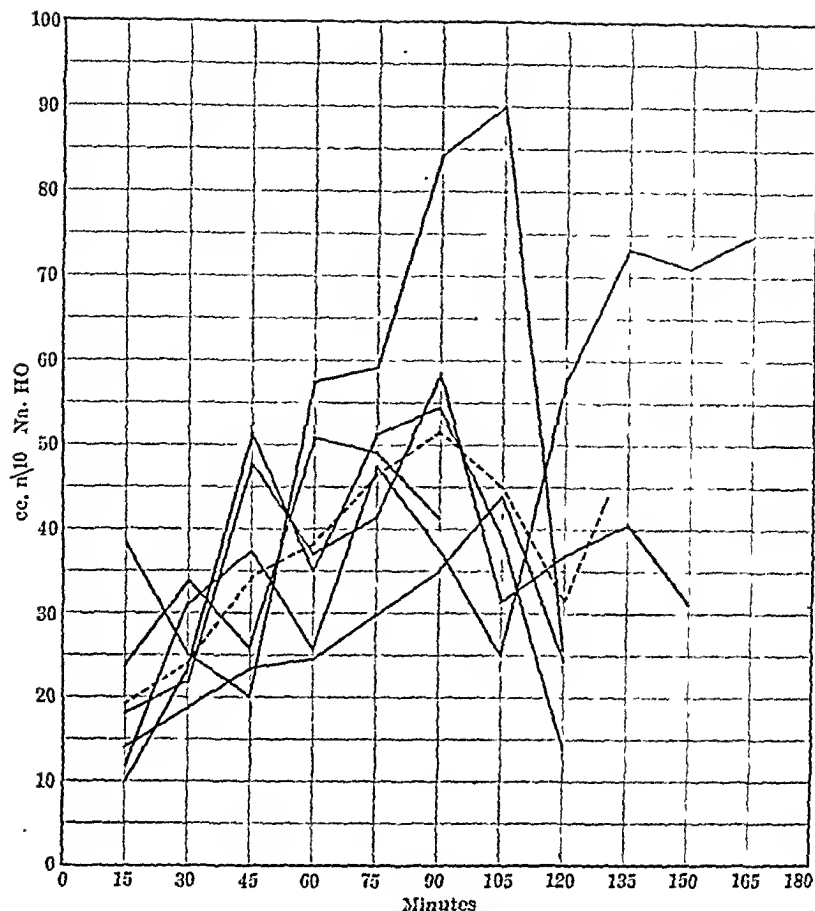


FIG. 4

TABLE IX.  
MOTOR FUNCTION.

Table.	Roentgen-ray.				Emptying time by fractional test meal.
	Tone.	Stoma.	Peristalsis.	Empty in.	
1	Good	..	Active	5½ hours.	2 hours, 5 minutes.
6	Good	..	Very active	6½ hours	2 hours, 9 minutes.
7	Fair	..	Moderate to fair	5½ hours	2 hours, 22 minutes.
8	Good	..	Active	6 hours	2 hours, 5 minutes.

CHEMISM.

Table.	Fasting contents.			Ewald test-breakfast.			Riegel test-meal.		
	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.	Residue in cc.	Free acid.	Total acid.
1	0	..	..	50	35	59	0		
6	37+	17+	30+	115	20	48+	10	18	31
7	26+	26+	53	177+	36+	63+	46	22	44+
8	11	6	17	100	31	65+	31+	48	69+

After a suture operation the roentgenographic evidence indicates that peristalsis becomes excessive and in some cases violent. Even with this increase in muscular effort, however, the total effect as regards the emptying time of the stomach does not show any appreciable advance over the preoperative status; in some, indeed, it is lengthened. When an exclusion has been practised the muscular effort gives evidence of some inhibition. In either case it seems that the total efficiency of the stomach as a machine whose function is to empty itself in a given time, is disturbed. With the button operations the roentgenographic evidence indicates that the contractions of the stomach wall most nearly approaches the preoperative normal standards, and the total efficiency seems least disturbed.

When considering these observations from the point of view of the kind of operation employed it becomes necessary to give much attention to the size of the stoma, to the ease with which stomach contents can engage in its lumen and pass onward in the alimentary canal, to the presence or absence of an open pylorus, and to the presence or absence of deformity of gastric contour. In the cases discussed in this communication no case with any deformity of contour has been included. The cases with spontaneously produced and preëxisting pyloric stenosis were also discussed previously. In the acute pyloric occlusion produced in the exclusion operation the evidence indicates that some disturbances may be expected owing to the fact that the stomach is not adequately prepared for this anatomic change; time must be given for complete compensatory readjustment.

The physical characteristics of the stoma are matters of importance in its proper functioning. It is important that no spur be created and that no superabundance of gastric mucosal folding be present and capable of falling across the mouth of the stoma with the formation of a valvular mechanism; in either case the passage of stomach contents would be impeded. The size of the stoma is most important. When studying the subject with the roentgen ray it is to be noted that in some of the cases the major portion of the contrast meal pours through the stoma in a large stream into the small intestine at a very rapid rate; the stomach is practically empty in a comparatively few minutes. In others of the cases a small amount remains in the stomach after the initial rapid outpouring of the contrast meal, and for some unaccountable reason takes a comparatively long time to be evacuated completely. Clinically the cases with such rapid outpouring and emptying frequently have distressing symptoms. In these cases the stoma is manifestly too large. Many experiences have indicated that a stoma which is too large is just as bad—if it be not worse—as one which is too small; a happy medium is desirable.

In fashioning the stoma with the button the finally resulting

opening is just large enough to admit an average-sized forefinger. This corresponds rather accurately with the size of the normal pylorus. The opening made with the suture method is always much larger than this; in most clinics the stoma is made large enough to admit easily two average-sized fingers. This means a very large difference when one takes into account the number of muscle and nerve-bundles divided; with the button a small incision is made and the latter is then bluntly dilated sufficient to admit the button; with the suture much more than two fingers' breadth must be cut in order to allow for subsequent contraction. I am inclined to think that for this reason the functioning of a button stoma shows a nearer approach to the normal standard; its action more nearly approaches that of the pylorus.

**Summary.** Evidence is presented which seems to show that the functional result of a gastroenterostomy made with the aid of a Murphy button is superior to that of a gastroenterostomy made by the suture method.

## THE MALE SEXUAL GLAND IN THE PREVENTION OF CREATINURIA.\*

BY MORLEY D. MCNEAL, M.D.

FELLOW IN PEDIATRICS, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

THE perplexing problems of the origin and intermediary metabolism of creatin and the factors influencing its excretion have not been definitely solved, in spite of the mass of investigative work. Creatin is found normally in animal tissue, specially muscle, in the urine of children, and occasionally in the urine of normal women. Only under certain pathologic conditions, such as fasting, cachexia, febrile disease, hyperthyroidism, diabetes mellitus, myopathies and so forth does the adult male excrete creatin. "Since creatinuria disappears at puberty, and does not occur in normal man, a hitherto neglected factor for its excretion obtrudes itself, namely, the influence of the male sexual gland."<sup>1</sup>

In order to determine the effect of castration on the creatin excretion of the rabbit, experiments initiated August 1, 1920, were carried out at the Sprague Memorial Hospital of Chicago, in conjunction with Dr. George H. Jackson, Jr. In some instances there was a pronounced increase of creatin excretion on the second day following castration, and possibly a slight persisting increase lasting forty-five days. These experiments were controlled by

\* This work was undertaken at the suggestion of Dr. S. Amberg, to whom I wish to acknowledge helpful suggestions given during the course of the study.

similar experiments on rabbits in which the vas deferens was tied off. The results were only suggestive at best. Such experiments should be repeated on animals that normally do not excrete creatin, as the onset of creatinuria gives results more definite than a condition in which the normal amount of creatin is increased. Such conditions exist in man.

Beginning in February, 1921, we have had the opportunity in the Mayo Clinic of studying the creatin excretion of two eunuchs, three men with a congenital testicular defect and one man with a defect acquired at the age of twenty-seven years. We had completed the rabbit experiments, the observations on one eunuch, and on one person with a congenital testicular defect, when the very interesting paper of Read appeared. Having the same idea in mind, Read had studied the creatin excretion of the Chinese eunuch; he found that creatin was constantly present in the urine of eunuchs who had been castrated before the development of the secondary sex characteristics. His results are tabulated:

TABLE 1.

Eunuch.	Age.	Age at operation.	Excretion of		
			Nitrogen, gm.	Creatinin, per cent.	Creatin, per cent.
2 . . . .	18	12	7.12	Trace	0.149
3 . . . .	18	9	4.09	0.204	0.424
4 . . . .	30	19	....	0.039	0.060
5 . . . .	27	?	....	0.006	0.017
6 . . . .	40	29	....	0.004	

The heading per cent, under which the creatinin and creatin values are given, we assume to mean total output in milligrams. The creatinin and creatin values are very remarkable. Read states that the absence of creatinuria in eunuch 6 is owing to the fact that castration was performed at the age of twenty-nine years, after the development of the secondary male characteristics. As the sexual maturity of the Chinese race is late, the infantile influence on creatin metabolism was still present in eunuch 4 at the time of castration performed as late as the nineteenth year. Therefore, he continued to excrete creatin for the same reason as eunuch 3, castrated at nine years.

In each of our six patients one specimen of urine was analyzed for creatin immediately after voiding; the results correspond with the subsequent determinations. The twenty-four-hour specimens of urine were collected in a bottle containing toluol and surrounded by ice. Folin's method was used for the determination of the creatinin and creatin and Folin's micro Kjeldahl method for the determination of the nitrogen. The patients were on a general diet, on which normal man does not excrete creatin.

## REPORT OF CASES

CASE 1.—(A344023) H. E. B., aged thirty-one years, was unmarried. He had been in good health, and normal sexually, until February, 1918, when, following a therapeutic accident, it was necessary to remove completely the testicles, serotum, and penis. His libido remained. The patient was muscular, and unusually fat around the face and neck; this had increased since castration. He was a blond, had very little hair on the body, but the normal amount on the head and face and in the armpits. He was treated for chronic granuloma in the region of the operation. The analysis of his urine is shown in Table 2.

TABLE 2.

Month.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
5 . . . . .	8.59	1169	124.3
6 . . . . .	13.8	1535	115.0
7 . . . . .	9.53	1352	59.0
8 . . . . .	9.68	1518	52.8
9 . . . . .	11.99	1412	53.8
11 . . . . .	12.09	1190	137.3

CASE 2.—(A354881) W. D. E., aged forty-two years, had been married eleven years and had not had children. Sexual incompetence and a minimum of libido had always existed. His build was of the feminine type, with broad pelvis, hypotonicity of the musculature, and an accumulation of fat in the breasts and buttocks. There was no hair on the body, a normal amount in the armpits, and a scant growth on the head and face. He said that there had been scarcely any change in his appearance during the past twenty years. The testicles were pea-sized; the penis was small. The basal metabolic rate was -15 per cent. The analysis of the urine is shown in Table 3.

TABLE 3.

	April.	Nitrogen, gm.	Creatinin, mg.	Creatin. mg.
	23 . .	6.13	1221	117.6
	24 . .	12.14	1446	98.6
	26 . .	23.18	1699	339.9
	27 . .	11.63	1428	140.0
Thyroid extract, 5 grains . .	28 . .	14.28	1500	192.0
Thyroid extract, 5 grains . .	29 . .	18.79	1433	75.4
	30 . .	7.59	1499	322.0
	May			
	2 . .	11.55	1584	561.0
	3 . .	8.31	1397	479.4

CASE 3.—(A330908) C. H. H., aged thirty-nine years, had been married five years and had not had children. At the age of thirteen

the testicles had been swollen and painful for a short time. At the age of twenty-seven a syphilitic infection occurred. For the last eight years sexual incompetence had gradually increased, becoming marked during the last two years. The beard and the hair under the arms had disappeared at the onset of sexual incompetence. The patient was masculine in build. The testicles and penis were small. The basal metabolic rate was -31 per cent. Polydipsia and polyuria had existed for several years and the response to injections of pituitrin justified a diagnosis of diabetes insipidus. The findings of the cerebrospinal fluid were those of cerebrospinal syphilis. The analysis of the urine is shown in Table 4.

TABLE 4.

March.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
5 . . . . .	7.67	1650	132.0
6 . . . . .	5.38	1347	73.6
7 . . . . .	6.85	1349	28.5
8 . . . . .	9.68	1518	52.8
9 . . . . .	3.23	555	49.5

CASE 4.—(A375931) R. N., aged thirty years, unmarried, had always been in good general health. Potentia and libido had never been present. His general build was feminine, with broad pelvis, narrow shoulders and a marked accumulation of fat in the breasts. He had no hair in armpits or on face, and it was sparse on the pubes. The testicles were pea-sized, and the penis about 2.5 cm. in length. The prostate was not palpable. His voice was high-pitched; he appeared to be about seventeen years of age. The analysis of the patient's urine is shown in Table 5.

TABLE 5.

July.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
19 . . . . .	11.9	1422	154.0
20 . . . . .	7.4	1230	98.0
21 . . . . .	9.6	1430	91.0

CASE 5.—(A367481) J. K., aged fifty-one years, had always been in good general health. Following a gonorrheal infection twenty-three years before, he had developed painful, chronic epididymitis, for which castration was performed four years before examination at the Clinic. He had been sexually normal, but after the operation libido and potentia were lost. The examination was negative except for moderate adiposity and evidences of a chronic prostatitis. The patient did not remain under observation long enough so that a twenty-four-hour specimen of urine could be obtained. The results of the analysis of two freshly voided specimens are shown in Table 6.



TABLE 6.

	Nitrogen, gm. for each 100 cc.	Creatinin, mg. for each 100 cc.	Creatin, mg. for each 100 cc.
Day specimen . . . . .	2.48	322	15.9
Night specimen . . . . .	3.89	247	6.3

CASE 6. (A375931) W. R. M., aged thirty-seven years, was unmarried, and had always been in good health. Libido and potentia had always been absent. He was very tall and thin, with narrow shoulders. He was well developed muscularly. He appeared youthful, and his voice was high-pitched. He had only a few hairs on the pubes and in the axillæ. The testicles were pea-sized and the penis very small. The basal metabolic rate was -10 per cent. The patient represented a typical picture of a eunuchoid giant. The analysis of the urine is shown in Table 7.

TABLE 7.

	October.	Nitrogen, gm.	Creatinin, mg.	Creatin, mg.
29 . . . . .		10.78	1800	98
30 . . . . .		12.46	1896	147

The men (Cases 1 and 5) who were castrated at the ages of twenty-nine and forty-seven years respectively, excreted creatin. This is in contradistinction to the observations of Read, who asserts that creatinuria occurs only in eunuchs in whom castration is performed before sexual maturity. Analysis of the urine of three men with congenital testicular defects, and of one with a deficiency acquired at the aged of thirty-one, showed the presence of creatin regularly.

We had hoped to report a parallel series of cases with loss of libido and potentia, on a functional basis, and not dependent on an organic defect. Unfortunately, we had the opportunity to study only one such person. He had been healthy and normal sexually until July, 1921, when he discovered on one testicle a small swelling (spermatocle). After that, libido and potentia were wholly lost. The physical examination was negative. Creatin was not found in this patient's urine.

**Discussion.**—The creatin output varied markedly in the same patient from day to day and bore no relation to the total nitrogen and fairly constant creatinin values.

It is of interest to note that during the observation of Case 2, particularly high creatin values were obtained following the administration of thyroid extract for two days.

It is to be noted that all the cases were free from any condition with which creatinuria in man had been described, such as hyper-

thyroidism, diabetes mellitus, cachexia, disease of the liver, febrile disease, or primary and secondary myopathies.

Besides the sexual incompetence on an organic basis in Case 3, a diagnosis of diabetes insipidus was made. In view of the fact that creatinuria occurs in association with diseases of three other endocrine glands (thyroid, pancreas, and male gonad), it seems quite possible that the disturbance of the pituitary gland may have exerted additional influence in the production of the creatinuria.

#### BIBLIOGRAPHY.

1. Amberg, S.: Abt's System of Pediatrics. (Not yet published.)
2. Folin, O.: On the Determination of Creatinine and Creatine in the Urine. Jour. Biol. Chem., 1914, 17, 469-473.
3. Folin, O. and Denis, W.: Nitrogen Determinations by Direct Nesslerization. I. Total Nitrogen in Urine. Jour. Biol. Chem., 1916, 26, 473-488.
4. Read, B. E.: The Metabolism of the Eunuch. Jour. Biol. Chem., 1921, 46, 281-283.

---

### A CLINICAL AND PATHOLOGICAL STUDY OF NEURITIS IN THE TROPICS, WITH SPECIAL REFERENCE TO BERIBERI.

BY WILLIAM E. MUSGRAVE, M.D.

SAN FRANCISCO,

AND

BOWMAN C. CROWELL, M.D.

RIO DE JANEIRO.

*Introductory Note.* This clinical and pathological study represents our crystallized opinions upon the principal problems connected with the subject, after prolonged residence in the tropics in teaching, research and practice.

No attempt is made to review the literature or to cover the practical field completely.

It is our aim to elucidate "Neuritis in the Tropics" rather than "Tropical Neuritis," and to clarify as much as may be this exceedingly difficult subject.

Of the problems of tropical pathology, that of neuritis is one of the most interesting, baffling and important. It is still very far from being solved.

The literature on the subject is enormous and much of it is of little value. Perhaps in no other field do we see so much uncontrolled, incomplete or unreliable work used as a basis for so many

varied and often unwarranted conclusions. On the other hand, splendid, careful research has been done both in the laboratory and clinical fields, and contributions are being made which tend to simplify the problem. In fact, in some of its most important phases solution is already in sight.

At the very beginning of our problem we encountered difficulties in classification. While we know that etiologically there is more than one disease in the group of the neurites, neither by a study of the clinical picture nor the pathology have we information which clearly distinguishes between some varieties of known etiologic difference, much less between those of unknown causes. Sometimes it even is exceedingly difficult to state that a given picture in reality is neuritis.

Nevertheless, the only sound classifications are those based upon etiologic grounds, and to do this we must at times accept hypotheses tentatively as facts or classify arbitrarily. The problem is more complex in the tropics than it is in temperate climates because of the great prevalence of the endemic neuritis, generally called beriberi.

We shall be guided in our discussion by the following outline:

### ETIOLOGICAL CLASSIFICATION OF MULTIPLE NEURITIS

#### A. *Intrinsic Factors:*

Heredity (anatomic, physiologic and social status).

#### B. *Physical Agents:*

Traumatism and pressure.

Meteorologic and climatic conditions (altitude, atmospheric pressure, heat, cold, moisture, winds).

Occupation, electricity.

Environment in general.

#### C. *Chemical Poisons:*

Inorganic (arsenic, lead, etc.).

Organic (alcohol, etc.).

#### D. *Intoxications:*

Exogenous—food and other substances already poisonous when taken, toxins formed in various ways in the alimentary canal.

Endogenous (excluding toxins of known biologic agents):

1. Toxins formed within the body and due to derangement of metabolism, in nephritis, anemia, etc.

2. Internal secretion disturbances.

#### E. *Biologic Agents* (including their toxins):

Animal—syphilis, malaria, hookworm, schistosoma, trypanosoma, etc.

Vegetable—tuberculosis, typhoid, diphtheria, undulant fever, leprosy, etc.

F. *Metabolism Disturbances Due to Faulty Food Balance:*

Neuritis in pregnant and parturient women.

Neuritis in nursing infants.

Endemic tropical neuritis, beriberi.

Most of the etiologic factors shown in the table, and which are concerned in the production of neuritis in other countries, must be reckoned with in a study of the disease as it exists in the tropics. The most careful direct search for the etiology in each case of neuritis and a diagnosis only after the most exhaustive study and elimination is specially urgent in the tropics, and, if done, will give two very desirable results: It will change the present custom of diagnosing practically all cases of neuritis as beriberi, and it will result in simplifying the beriberi problem by harmonizing the results of investigation.

*Intrinsic Factors.* Conditions inherent in the patient, including hereditary influences and possible intrauterine diseases, must be important predisposing factors in at least certain classes of neuritis.

The report of the government committees for the investigation of infant mortality in the Philippine Islands records an average intrauterine death-rate of over 30 per cent. The causes of these deaths are in part at least unknown, and a predisposing influence to disease of the nervous system among those who do not die is generally recognized.

The anatomic, physiologic and social status as it has been evolved out of a poor heredity, disease and all but universal malnutrition might well be supposed to leave the nervous system particularly susceptible to neuritis as we know it leaves other parts of the body for other diseases. Indeed, histologists are frequently surprised in their study of supposedly normal histologic tropical material to find the nerves abnormal and even at times showing the picture of neuritis.

*Neuritis Caused by Physical Agents.* It is probable that physical agents are more important factors in the production of neuritis in the tropics than elsewhere. This may be due in part to special environment, and there are facts which indicate that neuritis may be produced in an Oriental by conditions which would rarely lead to such a result in temperate climates.

As an example, neuritis of the lower extremities is quite frequent during the latter months of pregnancy. In many instances the complication may be beriberi. Apart from this phase, which will be discussed under beriberi, there is a considerable number of these varieties that have little resemblance to beriberi. There are no cardiac symptoms or other evidences pointing to a serious condition. They appear to be due to pelvic pressure and to the water-logged edema of the dependent parts. This condition, noted but rarely in temperate climates, is quite prevalent in the tropics.

Neuritis from pressure by tumors, aneurysms and tight bands worn by certain tropical people is noted occasionally, and it sometimes follows the extensive traumatic wounds so frequently encountered in the land of the bolo and the kris.

Posture has been thought to be a factor in the preponderating prevalence of neuritis of the lower extremities over that of other parts of the body. Most Orientals rest in the squatting position instead of upon a chair, and they may remain comfortable in such position for hours at a time. Acosta-Sison considers this fact responsible for the very great prevalence of malpositions of the uterus among Filipino women.

Sudden changes from the lowlands to the cool high altitude hill stations is associated with the development of neuritis too often to be explained by coincidence.

Other meteorologic and climatic conditions influence the progress of neuritis, and the sudden changes so often seen in the tropics from hot and dry to cool and humid, although slight as compared with similar changes in colder countries, nevertheless produce most profound effects upon people and may not be disregarded in considering the onset of neuritis.

What in a general sense may be termed tropical environment exerts a powerful and constantly acting adverse influence upon the nervous system of all persons. Just what particular factor or factors in the environment are most to blame is not fully understood, but it is probable that it is the composite picture made up of heat, moisture, sudden change, mode of living, worries and fretting, and the squalor, ignorance, poverty, mixed languages and general unesthetieness of the whole thing—all acting together—that racks the nervous system of the foreigner and influences the propagation of the weak, emotional, unstable, hysteric type so general among Orientals. It perhaps would be going too far to say that these conditions are the actual causes of neuritis, but that they so successfully prepare the way that otherwise innocuous agents may bring it about seems likely.

*Neuritis Caused by Inorganic Chemical Poisons.* The only known variety of particular importance in the tropics is arsenic neuritis, and the careful observer finds this quite frequently. At one time arsenic was considered to be a cause of beriberi. Arsenic is used extensively by many of the dark-skinned races as a medicine to be taken internally and in lotions and powders for the skin. Its skin-bleaching properties are widely known, and frequently enormous amounts are used to lighten the color of the skin, which is the vain ambition of every native woman.

Lead paints and lead work in general is not extensively applied in the Orient and lead neuritis rarely is seen.

*Neuritis Caused by Organic Chemicals.* Alcoholic neuritis is the most prevalent type in this group, just as it is in other countries.

It is generally stated that tropical people are not important consumers of alcohol. This oft-repeated statement is open to serious doubt. Imported and taxable alcohols for beverages average about three-eighths less per capita in the Philippine Islands, for example, than in the United States. However, in making comparisons it must be remembered that the average size of Orientals is only a little over two-thirds that of Americans, that their nervous systems are more sensitive and that the effects of alcohol upon any person is greater than it is in a cold country. Furthermore, the most prevalent alcohols consumed by the great mass of Orientals are not taxable and not therefore included in statistics. There are a considerable number of home-made preparations of alcohol, from the palm, sugar cane, etc., that are just as effective, probably more so, in producing neuritis as the imported varieties.

In any event, alcoholic neuritis is quite frequently seen in our large clinics among all classes, and in most instances a tentative diagnosis of beriberi is made. A supposedly typical case of beriberi was used in a clinic for senior medical students. The instructor felt humiliated when positive evidence was secured that the patient was a gin-drinker and had averaged nearly a quart of gin a day for several years.

Neuritis due to the other recognized organic chemicals is not frequent enough to be of importance. However, there is a great practically unexplained field among the unknown local herbs used as medicine. Practically all Orientals are extensive users of "herbs" as medicine. Most trees, flowers, weeds, as well as many fish, insects and minerals, are included in this group of cure-alls. Some of these substances are known to contain active poisons, and many others no doubt belong to the same group.

*Neuritis Due to Intoxication.* Toxins introduced in food or formed in and absorbed from the alimentary canal are a vastly more important subject in the tropics than elsewhere. That neuritis may be caused by such direct intoxication seems likely. The activities of the great variety of capsulated anaerobic bacteria constantly forming part of the tropical intestinal flora offers a promising field for investigation.

"Ptoomain" poisonings are exceedingly common, and the enormous prevalence in the tropics of intestinal derangements due to infections and to the questionable quality of much of the food eaten by the poor makes it likely that this subject is more important in the etiology of neuritis than we now realize.

*Endogenous toxins* formed as products of disease or from deranged metabolism caused by disease assumes special importance in the tropical problem of neuritis. In addition to such diseases as diabetes, rheumatism and nephritis we have an unusual number of anemias, cachexias, fevers and other pathologic conditions of unknown cause which are not infrequently forerunners of neuritis.

The recognized excess of lymphoid tissues, forerunners of the hyperactivity of ductless glands and consequent instability of internal secretions, constitutes an enticing field for tropical investigation, and is looked upon with suspicion as an influence in the production of tropical neuritis.

*Neuritis Caused by Biologic Agents.* Animal parasites, such as those causing syphilis, yaws, malaria, trypanosomiasis and schistosomiasis in particular, acting either directly or through their toxins, are the exciting causes of a certain percentage of neuritis. Other animal parasites, including the various intestinal worms, exert a pronounced effect upon the nervous system, particularly in children, and it is probable that they at times may be considered the exciting cause of neuritis.

Bacteria and other vegetable parasites which cause tuberculosis, leprosy, pneumonia, typhoid, influenza, whooping-cough, undulant fever, and gonorrhea in particular, are recognized as the exciting causes of neuritis. In this role they may act directly, as in the case of the leprosy bacillus, or indirectly through their toxins, as shown for example in the diphtheria toxin.

The unknown causative agents of certain other diseases, as small-pox and dengue-like fevers, also must be considered among the causes of neuritis.

As in the well-known cause of typhoid neuritis the bacteria must not bear the entire blame for the neuritis, which in reality often is due to the action of the bacteria in the presence of a nutritional deficiency caused by insufficient or improper food.

*Incidence.* The various forms of neuritis discussed up to this point have a much higher incidence in the tropics than is generally recognized. Except in clinics and in hospitals there seems to be a remarkable tendency to diagnose all of them as beriberi without further investigation. During one period of about six months a careful study of patients admitted to our service with a previous diagnosis of beriberi showed over 50 per cent of them to belong in other groups.

The clinical varieties of acute, chronic and residual conditions seen in neuritis elsewhere are found among those in the tropics. The clinical picture otherwise, as well as the pathology, prognosis and treatment, do not differ sufficiently from similar conditions in temperate climates to warrant special attention here. Diagnosis is more difficult, much more difficult, and will be considered in the discussion on beriberi.

After we have studied a series of cases of neuritis in a tropical community by all the means at our command, and have classified them as far as possible into groups of known causes, there still remains a very large proportion unaccounted for, and these we will consider under the most used name of beriberi.

## BERIBERI.

## Synonyms—Definitions—General Remarks.

*Predisposing Causes:*

Inherited and prenatal factors (breeding, constitution, temperament, etc.).

Physical factors (climate, meteorology, geography, etc.).

Social factors (age, race, sex, poverty, etc.).

Public health factors (sanitation, overcrowding, prisons, etc.).

Personal hygiene and personal health factors.

Incidence, predisposition and immunity.

*Exciting Causes:*

Brief review of the various theories.

Discussion of the various theories.

As a group disease.

Summary of present knowledge, conclusions.

*Pathological Anatomy.**Symptomatology* (introductory remarks):

Clinical types: Acute, chronic, rudimentary, residual conditions.

*Complications* (diagnosis, prognosis).

*Prevention* (public health measures, personal measures).

*Treatment.*

*Synonyms.* Kakke, asjike, loempe, endemic multiple neuritis, panneuritis endemica and many, many others.

*Definition.* A chronic or less frequently acute disease or group of diseases caused in whole or in part by faulty food supply, assimilation or metabolism. It is characterized pathologically by a multiple neuritis selective in type for the pneumogastric, phrenic, anterior tibial and peroneal nerves, but extending to other nerves as well; expressed clinically by edema, pain, paresthesias and absence of reflexes, particularly in the lower extremities, palpitation and dilatation of the heart, epigastric distress and absence of fever. It is endemic in most Tropical and Oriental countries and finds its highest incidence among the ignorant and exceedingly poor.

*General Remarks.* Beriberi is one of three or four diseases which, taken together, always have stood as an insurmountable barrier against progress, civic, economic and social, throughout the great Tropical and Oriental world. It is a large factor in the physical imperfection, mental primitiveness, social degradation, economic squalor and sanitary backwardness of the population of these countries. The history of the disease is well told in Vedder's excellent monograph on the subject. It has been known and something of its ravages recognized in China, Japan and probably elsewhere almost since the beginning of the Christian era. Practically no Oriental, Tropical or far-eastern country ever is free from



it. It occurs sporadically, endemically and pandemically. Without being contagious or infectious, it rises and falls and passes in great waves over vast territories of hundreds of millions of inhabitants. Its association with ignorance, squalor and poverty is so close and intimate that its statistical diagram might be taken as an index of the intelligence and progress of a community.

*Predisposition and Immunity.* Certain races appear to have a natural immunity against the disease, and certain of the Tropical races seem to be especially susceptible to it. Newcomers into a beriberi zone, whether of foreign or native birth, seem to be less susceptible in certain instances, while in others similar change appears to increase the risk to the immigrants. It is probable, however, that all of these observations may be satisfactorily explained by other forces than predisposition and immunity. One or a number of attacks of the disease does not produce immunity, and it is likely that no such quality exists.

*Etiology (Predisposing Causes), Prenatal Influence.* We have not sufficient evidence to justify a positive statement that there is anything in inheritance or prenatal disease which predisposes to beriberi. However, the frequency of the condition in infants and other facts point to the existence of some such influence.

The frightful infant mortality in all tropical countries, due in large part to the poverty and squalor of the people and the consequent physical unfitness of mothers, and particularly the sacrifice of intrauterine life from similar causes, which constitutes over 30 per cent of the fetal death-rate in the Philippine Islands, strongly suggests that prenatal conditions are in part responsible for the high incidence of beriberi under certain conditions and among certain people.

*Physical Conditions.* Beriberi finds its highest incidence under certain physiographic conditions, climate and rainfall, and is largely confined within certain geographic limits.

Environment favorable to the spread of beriberi is that generally described as the East, the Orient or the Tropics. This does not necessarily mean climate, heat, geography, rainfall, customs of the people, activities, energies or any other one thing, but a conglomeration of these and many others which molds all classes who dwell in it to a something in common or destroys them. This environment is the home of beriberi, as it is of so many other diseases and abnormalities.

The disease is common in the entire Malay Archipelago, India, Burmah, Ceylon, China, Japan, the Philippine Islands, Dutch Indies, Korea, Siam, New Zealand, Australia, Africa, South Sea Islands, South America and on ships in various seas. In some countries it is limited to certain areas, and outbreaks are recorded in many parts of the world.

Seasonally, beriberi appears to be a wet-weather disease. In

endemic areas it is found at all times of the year, but in most places from which we have reliable statistics it reaches its highest incidence during and just after the rainy season. There are exceptions to this rule, and in some locations variation in rainfall is not sufficient to warrant emphasis on the wet season. In the Philippine Islands the incidence curve is highest toward the end and shortly after the rainy season, but the difference is not striking, and some of the past epidemics have continued through more than one season.

*Other physical conditions* which seem to be associated with the prevalence of beriberi are shown in its selection of lowland and river valleys, being less prevalent in high altitudes and in interior cities.

*Social Conditions.* The disease may occur at any age and in both sexes, but it is much more prevalent among young adult males and during early infancy. It is rare among very old people, and, except the infantile variety, it is less frequent during childhood. While all races are susceptible the dark-skinned tropical people are the greatest sufferers, and in given localities certain nationals seem more susceptible than others. Thus Bradden notes that while the native Malayan suffers but little, Chinese immigrants in the Straits and Malay Archipelago show a high incidence and a high mortality rate. In the Philippine Islands the native Filipinos are the greatest sufferers, the Japanese come next, and the disease is comparatively rare among the Chinese. Members of the white race rarely contract the disease.

*Occupation.* The disease is rare in all countries among merchants, artisans, professional men and in general among members of the social upper strata. It reaches its highest incidence among teamsters, farmers, rice-workers and others of the unskilled-labor classes.

*Poverty.* Beriberi is *par excellence* a disease of the poor, ignorant and superstitious, and is comparatively rare among any other class in any country. The poverty factor of greatest importance is that of quality and quantity of food supply. Poor people buy and eat almost without question what their local community markets supply, and this varies in volume, nutritional value and balance, always being deficient in proteins and fats.

*Public Health Conditions.* Beriberi subjects, regardless of race or residence, belong largely to the class who constantly infringe every sanitary requirement. They are mostly residents of the slums of the great Oriental and tropical cities, which means the worst that can be imagined for human beings. The worst areas are most frequently located on low shore land, with dirty, crooked, unpaved alleys for roadways, without any or with inadequate water supply or appropriate means for handling sewage and garbage. House construction is of the adobe stone without proper foundation or elevation, with dark, damp, poorly ventilated rooms, shared by human beings and animals alike; or, in certain other

localities, house construction is of bamboo or grass. Water is carried from a distance and stands in dirty barrels or earthenware pots; the local markets are dirty and the insect-covered and dust-covered food handled and examined freely by the different purchasers.

*Overcrowding.* Overcrowding is the rule in the slums of all Oriental cities. House-sleeping capacity is measured frequently by as many persons as may have pallet room on the floor, both sexes, children, sick and well, sleeping together indiscriminately in closed rooms. Only too frequently public buildings, such as barracks, prisons, theaters, amusement halls, etc., are not much of an improvement on the home conditions of these people, and overcrowding in such places is the rule in many communities. Millions of people live under conditions where there is no such thing as cleanliness, as the Occidental understands the word, and where there is no such thing as health, as he understands the term. These conditions, with variations to meet local custom, give beriberi its highest incidence and are responsible for the former hypothesis that it was a *place disease*. Existence under such circumstances may well be a predisposing factor to any disease, including beriberi.

*Personal Health and Hygiene.* Other diseases are not known to predispose to beriberi. Aside from its prevalence among pregnant and parturient women, it attacks persons otherwise apparently in normal health as frequently as it does weaklings. However, various diseases and depressing influences, such as the acute infections, mental exertion, emotion and excesses of all kinds, are considered by Scheube and others as predisposing factors.

*Exciting Causes.* As in many another disease for which a definite cause has not been determined, the theories concerning the etiology of beriberi are almost as numerous as its investigators. Each of these theories has been valuable insofar as it has led to accurate investigation of particular phases of the disease and the conditions surrounding its onset and occurrence. In this way, the list of possible causes has been narrowed down to relatively few. Thus far study of changes produced in the patient by the disease has furnished little that throws light on the true immediate causative factor, although predisposing influences have thus been detected. Rather a study of the external conditions surrounding the patient, and especially a study of the epidemiology, including diets, has been fruitful in furnishing satisfactory working hypotheses, at least concerning the cause of the disease, its prevention and its treatment.

While it probably is true that the exact determining cause of beriberi has not yet been absolutely proved, yet we are of the opinion that our present knowledge is sufficient to render some of the theories as to its etiology of more than historic interest. Ven-

turing upon this assumption, we will be satisfied with a simple classification of the various theories and will make particular mention of only those which have been of importance in leading us to our present state of knowledge and those which are associated with the names of investigators whose names in themselves entitle their theories to our respect.

## THEORIES CONCERNING ETIOLOGY OF BERIBERI.

### A. *Intoxication:*

#### 1. Inorganic chemical.

(a) Arsenic: Ross.

(b) Carbon dioxide: Ashmead.

(c) Oxalate: Trentlein, Maurer.

#### 2. Organic.

##### (1) Vegetable.

(a) Spoiled rice: Braddon, Fletcher, Breandat, Gelpke.

(b) Ptomaines.

(c) Other poisons.

##### (2) Animal.

(a) Fish: Gelpke, Mura, Grimm.

#### 3. Undetermined: Manson.

### B. *Infection:*

1. (a) Bacterial (definite): Pekelharing and Winkler, Sangerfield, Durham, Rost, Van Elcke, Okato and Kokubo, Musso and Morelli, Taylor, Wright, Wheate.

(b) Bacterial theory but not any recognized one: Manson, Castellani, Arnold, Baelz, MacGilchrist, Stanley, Daniels, Pearse, Lovering, Schubert, Balz, Legendre, Lovelace, Scheube, Shibayama, Marchoux, Travers.

2. Protozoan: Glogner and Heavley, Hewlett and de Koste, Fajardo.

3. Nematodes: Noc Kynsey.

4. Fungi: Rose.

### C. *Deficiency in Diet:*

Phosphorus: Schaumann, Aron.

Nitrogen: Takaki.

Potassium: Fales (and green vegetables).

Proteins and fat: Van Leent.

Poorly balanced, monotonous and inefficient diet: Vordermann, Braddon, Fraser and Stanley, Eijkman, Grijns, Highet, Nocht, Woolley, Chamberlain and Vedder,<sup>1</sup> Strong and Crowell, Heiser, Kilbourne, Hunter and Koch, Holst, Frohlich, Herzog, Gimlette, De Haan, Little, Darling,<sup>1</sup> Funk,<sup>1</sup> Williams,<sup>1</sup> Gibson.<sup>1</sup>

<sup>1</sup> Specific vitamin.

As indicated, beriberi occurs for the most part in tropical countries, and the classification given above indicates that practically all the theories that have been advanced recognize that the disease depends on the nature of ingested material. This is true whether the ingested material be harmful through insufficiency, through intrinsic poisonous properties or through forming favorable conditions for the development or growth of harmful material in the intestines. Almost all of the champions of the bacterial origin of the disease, among whom Wright holds a prominent place, consider the alimentary tract to be the portal of entry. Wright does consider wound infection a possibility and Manson doubts that it is a food infection.

Aside from those who have described definite microorganisms as the cause of the disease there are others who believe that bacteria, protozoa or fungi may produce changes in the food before consumption, and those who favor the idea that the food forms a favorable medium for the growth of organisms either before or after ingestion.

Concerning the theories which consider inorganic chemical poisons as etiologic factors in this disease, it may be said that very little evidence in their favor has been deduced; they do not furnish a satisfactory explanation of the clinical or pathologic phenomena of the disease, and they have met with no general acceptance among workers on this subject. The same may be said of the theory of ichthyotoxismus and lathyrism.

*Infectious Theory.* Among the workers favoring the infectious theory there may be said to be two classes:

First among these are the ones who claim to have isolated organisms to which they have assigned an etiologic role; these may be dismissed from consideration at the present time, as none of their work has been confirmed or generally accepted.

The second class is an important one and includes those who, from a study of the epidemiology, symptomatology and pathology of the disease, consider that it is best explained by an infectious theory without themselves indicating any special organism as the one at fault. Their reasoning is largely by analogy with known infectious diseases. In a long list this group includes the names of such distinguished workers as Manson, Scheube, Wright and others.

Manson believes that the disease is caused by the introduction by inhalation or otherwise of a toxin generated by some germ without the body. This germ, he believes, may be carried by man from place to place. He considers beriberi especially a place disease.

Scheube's reasons for considering beriberi an infectious disease may be briefly summarized by stating his emphasis on its occurrence in strong, well-nourished young persons, its geographic restrictions,

its seasonal occurrence, and on his belief that it cannot depend on deficient nutrition.

Wright drew attention to and emphasized the changes in the stomach and duodenum, and he maintained that these are the seat of growth of an organism which produces an extracellular diffusible toxin, and this causes the lesions and symptoms of the disease.

Those theories which ascribed an etiologic role to nematode parasites have never been given serious consideration. A protozoan cause has never been proved, although protozoa have been found by some to be associated with the disease.

*Diet.* From the earliest time a relation has been noted between diet and beriberi. In the search for the true cause almost every conceivable relation between diet and the disease has been investigated. Especially has its relation to the consumption of rice occupied an important place in the history. In turn, workers have considered the chemical constituents of the varieties of rice, the time and degree of its decortication, the time and manner of its curing and preparation for consumption, the way in which it is stored, the length of time it is stored, the changes occurring in it while stored, and the amount eaten.

The names of Eijkman, Vordermann, Grijns, Braddon, Fraser and Stanton, Heiser, Strong and Crowell, Highet, Chamberlain and Vedder and Funk and some Japanese workers should especially be associated with the growth of knowledge concerning the relation of diet to beriberi. (Omission of names from this list is not intended to belittle the value of an investigator's work, but the list obviously has grown too large to be given complete.)

Some of the ways in which diet has been conceived to be related to the disease are indicated above. The theory which now attracts most attention and seems most plausible is that which regards highly polished rice as an exclusive or almost exclusive article of diet to be deficient in a substance or substances necessary for metabolism. The first step toward the proof of this theory was to establish the fact that the consumption of decorticated rice was followed by beriberi. This has been proved experimentally in man by Fraser and Stanton and by Strong and Crowell. It has also been shown by others on larger scales, as by Braddon, by Vordermann and by Heiser in Bilibid Prison and in the Culion Leper Colony, where substitution of partly decorticated rice for completely decorticated rice led to the practical disappearance of beriberi.

Animal experimentation also has been of great value in advancing our knowledge of this disease. Eijkman in Java noticed the development of polyneuritis gallinarum in fowls fed on decorticated rice, and this work was soon confirmed by Grijns and others. The similarity between polyneuritis gallinarum and human beri-

beri was noted, and much fruitless discussion has been waged concerning their identity. It is sufficient to consider the two conditions analogous and apply truths elicited from a study of the fowl disease to man with caution. In this way it has been found possible to further our knowledge concerning the cause, prevention and treatment of the disease. It has been shown that fowls fed on fully decorticated rice develop polynuritis, whereas those fed on slightly decorticated rice do not. From this the idea arose that a neuritis-preventing principle is present in the husk of the rice. It has been found, especially by the United States Army Board for the study of tropical diseases as they exist in the Philippines, that extracts of this husk (so-called rice-polishings; in Tagalog tiqui-tiqui) if given with decorticated rice will prevent the onset of the disease or cure it when present in fowl. This extract has also been found of value in the treatment of human beriberi, especially in the infantile form. Attempts at further purification of the neuritis-preventing principle have been made by Funk, Vedder and Williams, Edie and his co-workers, and Susuki, Shimamura and Otake. These workers have obtained substances with different chemical formulæ, so that it cannot be considered that the essential principle has been identified. Funk has given the name "vitamine" to the hypothetic substance which constitutes the neuritis-preventing principle. This had previously been shown to be alcohol-soluble by Chamberlain and Vedder.

Other articles of diet available to the poor in beriberi zones have been analyzed and tested as to their content of neuritis-preventing principles, and with great and often surprising variations. Furthermore, the nature and importance of "vitamines" in diseases other than neuritis have developed rapidly, and new facts that may be of value in the study of beriberi are being accumulated in many places.

**Pathology.** The condition of the general nutrition of the beriberi patient varies with the stage of the disease and possibly with its type. In the early stage the general nutrition may be good, while in the protracted case marked emaciation may occur. Attention has been drawn to the fact that in the so-called "wet" type of the disease the anasarca may conceal a poor state of general nutrition. It must also be noted that a good general state of nutrition may not indicate well-nourished nervous tissues.

**Edema.** All of the tissues may show a marked edema, and this is manifest by subcutaneous edema which may be widespread, or, in the early stages, confined to the lower extremities, by ascites, hydrothorax, hydropericardium, meningeal and pulmonary edema. Numerous explanations have been offered for the edema. It appears early in the disease and obviously before any renal or cardiac insufficiency is demonstrable. It also occurs in cases in which the anemia is insufficient to account for it. Degenerations

in the *nervi vasorum* have been demonstrated as well as degenerate muscular and intimal changes in the vessels. It seems probable that the edema is to be accounted for by some pathologic change in the vessel walls.

*Heart.* Hydropericardium may be relatively greater than transudation into the serous sacs, or at times may not be present at all. Herzog found hydropericardium present in 66 per cent of 256 cases collected from the literature. Epicardial ecchymoses are almost always present. Enlargement of the heart is the rule. In the acute pernicious type this enlargement is due to dilatation, especially of the right chambers. In the more chronic cases hypertrophy also occurs and the hypertrophy of the right ventricle is characteristic. Left-side hypertrophy may also occur, but is much rarer. A groove can usually be seen at the apex between the two ventricles. The heart muscle shows parenchymatous degeneration and edema, and may show fatty change. Fragmentation of the muscle fibres and hyaline degeneration have also been described. Nagayo has seen hyaline and fatty degeneration involving the bundle of His. Scheube, Balz, Pekelharing and Winkler have described small myocarditic foci such as are found in diphtheria and other infectious diseases. Scheube has seen cellular infiltration in the subepicardial tissues and small hemorrhages in the heart muscle and beneath the endocardium. Explanation of the cardiac hypertrophy, and especially its usual restriction to the right ventricle, is difficult. Most arguments advanced in explanation in no way elucidate it. Matzuoka's theory appears to us the best, namely, that it is dependent upon the congestion-edema of the lungs. The origin of the pulmonary edema has already been referred to as due to changes in the pulmonary vessels. Degeneration of the intramural cardiac nerves also occurs.

*Lungs.* Transudation into the pleural sac occurs, but is usually not extensive. The lungs show congestion and edema, usually most marked in the lower lobes. This may be sufficient to lead to splenization. Emphysema of the apical portions and free anterior margin is not uncommon. Aspiration bronchopneumonia sometimes occurs.

*Liver.* Congestion of the liver forms a part of the general visceral congestion and may advance sufficiently to give the nutmeg appearance. Parenchymatous and fatty degeneration occur as sequels of the congestion. Nagayo has described an excess of glycogen in the liver.

*Spleen.* No characteristic changes occur in the spleen in beriberi other than those due to passive congestion. The markedly enlarged spleens which have been described in beriberi are undoubtedly due to other causes.



*Kidneys.* These organs show the effects of passive congestion and parenchymatous degeneration. Fatty degeneration also sometimes occurs. A glomerulonephritis has been described in beriberi by Miura, but it is a fact that the kidneys in this disease show relatively slight changes, and these changes do not account for the edema. Other symptoms of renal insufficiency, such as albuminuria, are not the rule in beriberi.

*Stomach and Intestine.* Wright drew attention to and emphasized the changes occurring in the stomach and intestine. He says: "The stomach and duodenum are toneless, dilated and empty. Their mucosa is deeply congested, rugæ and valvulæ are flattened and present numerous small hemorrhagic injections. Rings and patches of brilliant congestion occur and prove to be markedly dilated capillaries. They suggest sprinklings of red pepper. This congestion and ingestion may be found as low as the cecum; in a few instances I have found it in the ascending colon. As a rule it is most marked and occasionally wholly confined to the pylorus and duodenum. A thin pellicle of treacle-like mucous has occasionally to be stripped from the congested mucosa, but no true membrane is ever formed. Infrequently the congestion proceeds to hemorrhagic erosion of the gastroduodenal mucosa. The first chain of mesenteric glands is usually swollen. Microscopically the gastrointestinal mucosa exhibits all the signs of an acute inflammatory process." Here it is that he found his Gram-positive bacillus to which he ascribed an etiologic role. In his cases of beriberi residual paralysis he says, "The stomach and small gut are generally slightly dilated, but there is a complete absence of the gastroduodenitis seen in the acute stage of the disease."

In addition to the changes described by Wright, we have found frequently in the acute cases a very marked edema of the mucosa of the stomach and upper part of the small intestine. Intestinal parasites, to which an etiologic role has been assigned by some, have been no more frequent in our cases than in a similar class of patients suffering from other diseases.

*Adrenals.* Nagayo has described a progressive hypertrophy of the medulla of the adrenals in beriberi. In some of our cases a relative prominence of the adrenal medulla has been noted, but this has not been found as a constant feature.

*Thymus.* Nagayo has also noted enlargement of the thymus in beriberi. Funk and Douglas maintained that among the changes which take place in pigeons suffering from polyneuritis as a result of an exclusive white-rice diet a marked diminution in size occurs in the glands of internal secretion. His most marked change was in the disappearance of the thymus; macroscopically no thymus could be seen in any of the pigeons with polyneuritis. Following these observations a theory that a severe change in the glands of internal secretion occurs in beriberi has been proposed by Funk

on the *a priori* ground that the vitamins of the food have a close relationship to the glands of internal secretion. Williams and Crowell concluded on experimental evidence that there is no fundamental connection between beriberi and atrophy of the thymus, and that when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause. So in our autopsy records of adult beriberi humans it is found that the thymus gland is usually small. Crowell has already drawn attention to the occurrence of enlarged thymus in some cases of infantile beriberi and its association with status thymicolymphaticus.

*Pancreas.* No change in the pancreas has been described as characteristic of beriberi.

*Lymphatic Tissue.* Nagayo notes the enlargement of the lymphatic apparatus and classifies it as a progressive (restorative) change. He says that the changes in the lymphatic tissues may be due to a poison. The lymphatic tissues of the body have been especially noted by us in our autopsy work, and no change in them has been found in beriberi unless associated with other stigmata of status thymicolymphaticus. We see no evidence which points to any unusual incidence of status thymicolymphaticus in beriberi.

*Muscles.* Beriberi has been defined as a neuromuscular degeneration. Following, or coincident with, the nerve degeneration there occur fatty, hyaline and colloid degeneration of the skeletal muscles. The muscle fibers become thin, lose their striation, become homogeneous and fragmented. Cellular infiltration and hemorrhages between and into the muscle bundles have been described. Marked atrophy of the muscles follows, with replacement of the muscle fibers by fibrous connective tissue.

*Nervous System.* To Scheube and Balz belong the credit of demonstrating for the first time that the essential lesion in beriberi is a degeneration of the peripheral nerves. The degeneration may be present in the central nervous system, but is most prominent in the peripheral nerves. According to Scheube, sensory and motor nerves to the muscles are most affected in the dry or atrophic form of the disease, vasomotor nerves in the wet or hydropic form and the vagi in the acute pernicious types of the disease. The nerve endings in the muscles, as well as the nerve stems, are affected. Changes have been described in the vagi and phrenics, in the splanchnics and their visceral branches, in the solar and renal plexuses, in the nervi vasorum, in the cervical sympathetic ganglia, in the cutaneous nerves and in the nerves of the extremities. The changes occurring in the peripheral nerves do not seem to us different in type from those occurring as the result of various organic and inorganic poisons, such as in diphtheria and typhoid and in alcohol, arsenic and lead-poisonings.

According to Scheube the most severe changes are in the muscle branches of the nerves, and the main nerves show slighter changes.

In general, he believes the grade of degeneration corresponds with the paralytic symptoms, the most severe changes occurring in the chronic cases, while acute cases may even die before degenerative changes are demonstrable. It has been held by some that the process originates in the peripheral nerve endings and extends centripetally, but this requires demonstration.

The change that occurs in the nerve is first a degeneration of the myelin sheath with its conversion into a fat-like substance that stains black with osmic acid. Within the neurilemma are seen globules of this degenerated myelin which may distend the neurilemma and give a beaded appearance to the nerve. At other places these globules are smaller and the neurilemma is not filled. The globules may be vacuolated and foamy in appearance or a long area of the myelin sheath may appear uniformly black and wavy after osmic impregnation. The degeneration is accompanied by a fragmentation of the axis-cylinder, which in appropriately stained preparation may be seen in comma-shaped or S-shaped fragments within the masses of degenerated myelin. Eventually the neurilemma sheath may entirely collapse and it may show a multiplication of nuclei which is interpreted as an effort toward regeneration of the axis-cylinder. Degeneration fibers in a nerve may be very numerous, or only a few may be seen in the small part of the nerve usually submitted to examination, while the other fibers appear intact. Durck has demonstrated tyrolysis and vacuolation of the ganglia cells in the anterior horns of the spinal cord and in the spinal ganglia.

Degenerations have also been described in the fibers of the columns of Goll, Burdach and Clarke in the nuclei of the funiculus gracilis and funiculus cuneatus. According to Wright the cells of the bulbar nuclei and the nucleus ambiguus on both sides are swollen, with excentrically placed nuclei and a massing of the tigroid bodies.

Degenerative changes have also been demonstrated in the intrinsic ganglia of the heart, in the vagal nerve endings and in the nerve endings in other viscera.

Special attention has been drawn by Japanese authors to the degenerative changes in the nerves in the vessel walls. In the meninges congestion is the rule and small hemorrhages may occur.

**Symptomatology.** The clinical manifestations may be best understood by classifying them under four varieties:

1. Usual type.
2. Severe fulminant or pernicious type.
3. Chronic type and residual conditions.

*Usual Type.* The onset usually is somewhat insidious. The patient complains of a general feeling of discomfort or, as sometimes expressed, feels toxic. There is more or less epigastric distress which varies from a sense of fulness and indigestion to more

or less actual pain. The patient tires easily and there may be headache of a dull, heavy character. This prodromal stage may last from one to two or three days. Frequently the disease seems to be brought out during some slight indisposition, such as a "cold," diarrhea, slight fever or fatigue from prolonged exertion. In these circumstances there are no prodromal symptoms which may be positively charged to the neuritis. In any case the symptoms characteristic of the disease develop quite rapidly, so that the typical clinical picture is established within two or three days, although it may be delayed for a week. In the order of development the symptoms do not follow a fixed rule. Usually, heaviness, numbness and more or less pain develop in the legs. This is noticeable on walking, from which the patient quickly tires. Numbness and paresthesias develop first in the calf muscles, to be followed by pain on motion and tenderness on pressure. Edema, noticeable first as slight pitting over the lower tibia, progresses gradually over the legs and feet and later in other parts of the body, particularly the hands and face.

Usually the epigastric symptoms are considered to be indigestion, and, as a matter of fact, this frequently is the complaint which takes the patient to a physician.

As the disease progresses the leg pains become decided, particularly on motion or pressure; the joints feel as if they were out of control; the numbness may extend to the hands, arms and face; the edema becomes noticeable in the face and hands; a general sense of depression and oppression is complained of and the gait becomes characteristic of the disease. The altered gait is principally characteristic in that it is neither ataxic nor spastic, but more a combination of the two, and within a few days the patient is no longer able to walk or to stand without assistance.

The patellar reflexes at the very beginning frequently show a transient period of increased excitability, but they quickly become markedly diminished and finally lost entirely. The superficial reflexes usually remain normal.

In the fully developed disease the patient stays in a fixed position because motion increases the pain; the face and more or less rapid respiration indicate embarrassed circulation. The facies in general are those of an ill patient, the skin varying from normal to more or less cyanosis, the face, legs, feet, hands and frequently other parts of the body showing more or less edema; respiration and pulse are accelerated. There is epigastric distress, pains and tenderness in the legs and sometimes in the upper extremities. Numbness and paresthesias are unevenly distributed and more extensive than the pain areas.

The secretion of urine is diminished and there not infrequently is some looseness of the bowels. Nausea and even vomiting may be present.

Examination of a patient at this time shows tachycardia due to myocardial changes and influenced in some cases by more or less fluid in the pericardial sac. The rapid respiration may be due to embarrassed circulation, or there may be some fluid in the pleural cavities, and there may be a cough with considerable fluid expectoration.

There is tenderness over nerve areas, more marked in the calves, and usually pain is much increased on motion of the lower extremities. The patellar reflexes are absent. There is nothing significant to be found by examination of the urine or blood.

The patient may continue in this condition for days or weeks, with but slight change. In fatal cases the symptoms get worse, the pulse increases in rate, the edema extends, more fluid is found in the serous cavities and the patient finally succumbs to cardiac failure, less frequently to paralysis of respiration, or sometimes to acute pulmonary edema.

In patients who recover, the symptoms subside slowly, frequently but not invariably in reverse order to their appearance. As the circulation improves and the edema subsides the enormous muscle-wasting becomes apparent. Convalescence is exceedingly slow, lasting frequently for many months, and sometimes complete restoration of function never is attained.

There may be considerable variation in the clinical picture even in what we have termed the usual type. All of the symptoms may not be present in a given patient, and the order of their appearance may vary also. In one patient the epigastric symptoms may be the most pronounced and annoying, in another the cardiac symptoms may predominate, and there is frequent and marked variation in the extent and amount of the edema. In fact the edema may be so slight and temporary that the "dry" stage may be considered to be primary. Some authors consider that the dry form does develop primarily without there ever having been edema. However the matter is not considered one requiring lengthy discussion.

*Severe, Fulminant or Pernicious Type.* This type differs from the former chiefly in the intensity of the disease and the early and fatal heart failure. The onset usually is sudden. The whole cycle of the disease may be completed within one day, although the average duration is two to five days. It may develop out of a previously milder case.

This type of beriberi is a veritable plague, with very acute symptoms, a rapid course and practically always fatal. It rarely is encountered sporadically but occurs in prisons and in overcrowded places where the disease is epidemic. The nature of the symptoms and the order of their appearance frequently is much the same as in the usual type, but much intensified. The circulatory symptoms are the striking and characteristic features. They appear early and are the first and sometimes practically the only ones

present. At first there is tachycardia followed by increased respiratory rate, cyanosis, rapid heart failure and death. Edema of the lungs may constitute the terminal condition.

From first to last the clinical picture may not be distinguishable from that of acute progressive heart failure due to myocardial insufficiency from other causes. The expression is anxious, skin moist, eyes staring and pupils dilated, heaving chest motion and diffuse palpatory thrills.

Epigastric distress with vomiting is an early, severe and constant symptom. When the disease is a little less malignant and patients live more than two or three days the clinical picture may approach more nearly that given for the usual type. The edema has time to develop and the clearer intelligence allows a keener appreciation of pain and other subjective symptoms. The accumulation of fluid in the serous cavities is noticeable, the urine diminished, and there is thirst and loss of appetite.

*Mild or Rudimentary Type.* The onset is insidious. The earliest symptoms consist in a feeling of languor, a dull, stuffed sensation in the epigastrium, heaviness, numbness and some tingling about the calves. The sensations in the legs frequently are more noticeable in the night or early morning, particularly during the cooler season, when after hot days there is quite a decided chill in the early morning hours. Examination of a patient at this time will reveal slight but definite tenderness of the calves, slightly exaggerated but more generally definitely diminished patellar reflexes and possibly some acceleration of the heart-beat. In the majority of instances the patient will show slight but definite disturbance in the gait, consisting of hesitation in lifting the foot and an uncertainty or delicacy or deliberateness in placing it on the ground again.

One rarely sees this stage in hospital or private practice, but in the outpatient clinics for the poor it is encountered with great frequency. Unless the disease advances beyond this point there may be a question as to whether or not it really is beriberi. Most of these patients are from teamsters, laborers, rice-workers and others whose occupation keeps them outside, and they attribute the condition to getting wet suddenly while being exposed to the heat.

As the disease progresses the pains in the muscles of the legs, particularly the calf muscles, become more pronounced. These pains are spasmodic—cramps—and during the intervals between pains paresthesias are more or less constant. There is often a constant soreness of the muscles, and weakness of the legs is complained of after a few days or weeks of the disease. Other symptoms are dizziness, increased by exposure to the sun or by close application of any kind; slight epigastric distress and frequently some slight nausea. *Objectively* not much is found. The calf muscles

and often other muscles are tender on pressure and the patellar reflexes are sluggish and sometimes absent. Edema is slight or absent and examination of the heart may be negative. The blood, urine and feces do not show anything definite.

The disease lasts from a few weeks to months and even years unless treatment is instituted. Under rest in bed or confinement to the house, appropriate food and a simple bitter tonic recovery is rapid. Apparently one attack does not confer immunity, but rather seems to increase the patient's susceptibility. We have seen the same patient with as many as three attacks in one year.

During the protracted period of invalidism the patients hobble about, eke out an existence in various ways and alternate in "cures."

Muscular spasms and cramps of the legs with some paresthesia, noted more during cool nights, is not by any means confined to the Orientals. Many Occidentals who have resided in the tropics for years are sufferers from it. In many instances the exceedingly mild condition takes on other symptoms which are definite and leave no doubt of the diagnosis of a neuritis.

*Chronicity and Residual Conditions.* Except in the acute fulminant type the natural tendency of beriberi is toward chronicity. It is primarily a long-drawn out, slow-acting process, with acute exacerbations and tedious recovery, blending often into residual conditions which may be permanent and always disappear very slowly.

Regardless of the manner of the onset and the presence or absence of edema we have in the chronic beriberics a large problem. The extent of incapacity varies from those slightly crippled with leg cramps and tachycardia on exertion to completely helpless invalids, emaciated and miserable with pain.

After all activities of disease have subsided the residual paralysis, muscle atrophy and cardiac hypertrophy and dilatation remain for long periods of time, and it not infrequently happens that complete restoration of form and function never takes place.

*Analysis of Symptoms. Gait.* The gait is characteristic principally in that it differs from the various ataxias and spastic gaits of well-known diseases. It differs somewhat in accordance with the nerves involved, and consequently the corresponding varieties of muscle atrophy. True ataxia is never seen, but a spastic gait resembling that of spastic spinal paralysis may occur during convalescence.

*Disturbances of Motor Function.* All stages of muscular inefficiency are encountered, from numbness and sluggish action in mild cases to complete paralysis in the severe prolonged cases. There is selectiveness and variety in muscular involvement corresponding exactly to the distribution of affected nerves. In the order of frequency the muscles of the feet, legs, hands and arms are involved. Beyond various muscles of the face and body those

of most importance and serious consequence being the diaphragm and heart muscles. The sphincters are not involved. The electric reactions are similar to those found in peripheral neuritis due to other causes.

*Vasomotor and Sensory Changes.* Paresthesias of many types and varying form from complete anesthesia to the most intense hyperesthesia always form a part of the clinical picture. Those most prevalent are localized anesthetic areas corresponding to the anatomic areas most involved in the disease. The lips and tongue are paresthetic, frequently without signs of muscular insufficiency. The physical conditions of cold, moisture, pressure, etc., that affect paresthetic areas apply here. In interpreting phenomena of anesthesia and paresthesia it is well to remember that usually our patients are among the most ignorant natives of the tropics, who appear to be less responsive to our ordinary testing methods, and unless care is used errors are liable, particularly in interpreting anesthesia.

Vasomotor dilatation of the superficial vessels of the skin may lead to the most pronounced perspiration, and rarely an erythematous blush in affected areas may be seen among the lighter-skinned patients.

*Alterations in Reflexes.* The patellar reflex may be increased for a brief period at the onset of the disease. In all established cases it is either decidedly diminished or more frequently entirely absent. Altered patellar reflex usually is one of the earliest symptoms to appear and among the last to be restored to normal after recovery from the disease.

*Circulatory Disturbances.* Tachycardia in varying degrees is a constant symptom. In mild cases it may be scarcely noticeable on resting and only shows an exaggerated reaction from the mildest exercise. In more severe cases it becomes a prominent symptom, justly causing great anxiety to the patient, who can feel the increased rate and labored action of the heart. Frequently there is precordial pain. The heart symptoms are due to myocardial changes, with dilatation more marked on the right side but later involving both ventricles.

*Edema* and the collection of fluid in the serous cavities to a greater or less extent occurs in most cases of the disease at one time or another.

It is not unlikely that the transudation and exudation are dependent upon some more or less definite factor in the course of the disease as yet unknown. The frequent presence of dry atrophy as opposed to edema may be a striking symptom throughout the course of the disease. The more or less complete transfer from "wet" to "dry" varieties in the same patient is not easily explained, except by assuming an as yet unknown influence in the etiology of the disease.



The accumulation of fluid in the pericardium or pleural cavity may be sufficient in quantity to cause serious consequences. The amount in the abdomen and elsewhere is smaller, but there usually is some in all serous cavities, at least in acute cases of the disease. The edema usually appears first in the feet and legs, hands and arms, then the face, and later in severe cases one sees a striking picture of general anasarca. Pulmonary edema is not an unusual form of termination of the acute disease.

*Fever* is not a symptom of beriberi, and when present is due to some associated condition.

The systolic *blood-pressure* is generally lower in the tropics, both among natives and foreign residents, than it is in temperate climates. Even taking this fact into consideration the records seem to show that beriberi produces a lowering in the systolic pressure. This was true in the experimental cases of the disease studied by Strong and Crowell.

*Blood* examinations by the usual laboratory methods show nothing characteristic of beriberi. What departures from normal there are may be explained by associated conditions. A number of writers have called attention to a relative mononuclear increase of varying degrees, but Chamberlain and Vedder and others have shown that the relative increase in the lymphocytes is a pretty general condition in the tropics.

*Alimentary System.* Epigastric discomfort or distress is frequently an early symptom—sometimes the very earliest in the disease. These symptoms are probably due in part to more or less disturbances in the duodenum and in part to interference with digestion. They may be entirely absent. Nausea and vomiting may be distressing symptoms in fulminant cases and are fairly frequent in less serious forms. Diarrhea and other symptoms of intestinal disturbances are not important.

*Urinary System.* The most important symptoms are the variations in the quantity of urine excreted. Frequently in severe types the quantity is much decreased, and it may cease altogether before death. At times in the dropsical form there may be a very marked increase in the quantity of the urine, a change usually simultaneous with the reabsorption of fluid from the edematous areas. There are no characteristic changes found in the urine on routine examination.

*Diagnosis.* In endemic zones there is usually no particular difficulty in arriving at a diagnosis of multiple neuritis. Unfortunately only too often the diagnosis of neuritis is accepted as synonymous with beriberi. The differentiation between beriberi and multiple neuritis of other etiology is not easy to make by direct examination, and is only justified after a painstaking and thorough investigation into the etiology of each case.

Beriberi is most frequently confounded perhaps with alcoholic

neuritis. This mistake is made easy by the unfortunate statement so frequently seen that Orientals do not take alcohol. There is no greater fallacy in print. The poor people consume very poor qualities of cheap spirits, gin or beer, and in addition different localities have many different crude methods of preparing alcoholic drinks.

Differentiation from various other cropsies and edemas ordinarily is not difficult. However, it seems advisable to call attention to the mechanical difficulties encountered in examining the reflexes in patients already with much edema, particularly of the legs.

*Prognosis.* The mortality rates, as in all other pandemic and epidemic diseases, vary greatly as reported from different countries, as well as from different localities in the same country. The mild form rarely is fatal, but it often changes, and quickly, to a more severe one with higher mortality, and this potential danger must be recognized. The acute fulminant type is practically always fatal. Mortality in the usual form varies from 2 per cent to 60 per cent as given by different authors and representing statistics from different endemic zones.

*Preventive Measures.* Whether considered from a public health, social or medical standpoint the prevention of tropical neuritis is a large and urgent problem. More than half the population of the world live within the endemic zone and the disease must be eliminated before great permanent progress will be made in the development of many countries.

Beriberi is essentially a disease associated with ignorance, squalor and poverty. The home *par excellence* of these conditions, and therefore the home of beriberi, is in the tropical and subtropical belts, with its hundreds of millions of ignorant, superstitious, poverty-stricken people who live in tropical filth and lead a hand-to-mouth existence without thought or care for the morrow, and only too frequently where efforts at improvement are received apathetically or are resented.

The task of providing the essential remedies of better homes, better food and cleaner living is a disheartening one. Temporary improvement may be achieved in local areas by organized government and other charities, but this further pauperizes the people and is an impossible permanent solution on a large scale from an economic standpoint. Compulsory control over the lives and activities of the people has been employed in places. It is an effort of doubtful utility and one certainly not free from danger. Permanent results may be achieved only by instilling the attributes of thrift, energy, cleanliness and physical development into the people. To do this would include the expenditure of large sums of money; require a firm, non-political government and the constant directing influence of skilled advice over a period of several generations. The energetic, thrifty, clean-living citizen is at present

a tropical exotic, and the propagation of a population of this class is unlikely. Certain things, however, may be done, and the most important is to secure by the best and most practical means applicable to any given community such improvement in the food supply as is possible. This may be done, as in the Philippine Islands, by teaching gardening in the public schools and stimulating the cooking and use of good home-grown foods.

There is no doubt but what "undermilled" rice is a safer article of diet than that with all of the pericarp removed, and under circumstances where it is practically the sole available foodstuff for the poor, every possible effort to secure its use should be employed. Enforced use of whole rice may, of course, be employed by the military and in prisons and certain other institutions under such complete control that the inmates have little to say about what they shall do or eat, but compulsion should not be attempted among a people who have a voice in their own affairs. The Philippine experiment illustrates this point: Although red rice is not delectable to a rice lover, it might have been made popular, just as the Bureau of Education made the use of maize popular, except for the great and widespread resentment created by endorsing its exclusive use among soldiers, lepers and prisoners.

Nations holding colonial interests within the endemic zone of tropical neuritis can render no greater service to humanity than by studying their local problems and applying methods that will ensure the universal use of a better and more varied diet than exists in those countries at the present time.

**Treatment.** The treatment of beriberi is symptomatic and specific. The vast majority of patients are too poor to buy medicines, and when they do succeed it is at the sacrifice of food for themselves and perhaps their children. A clean bed in a light sanitary room and proper food will cure more of these patients than medicine, and it is less expensive. A glass of milk is a better "tonic" than all the drugs in the pharmacopeia.

Among the better-class patients the refined methods of symptomatic treatment may be instituted. The circulatory, urinary and digestive functions should be watched. Strychnin, digitalis, atropin and various other heart stimulants have been recommended to guard against or relieve existing circulatory or respiratory embarrassment. They are of doubtful value. Absolute quiet in bed with an ice-bag over the heart will do much to prevent the necessity of treating urgent heart symptoms. Squills, citrate of potash and other similar remedies are used to relieve the diminution in urine secretion, but are also of doubtful value. Small doses of concentrated solution of magnesium sulphate are indicated when a laxative is necessary.

*Specific Remedies.* Quite a variety of drugs have had from time to time more or less vogue as specifics. It may be safely stated than none of them has any such properties.

Due largely to the researches of Funk, Vedder, Chamberlain and many others during the last few years, decided progress has been made toward a specific treatment of the disease by the use of appropriate foods and particularly by the use of extract of rice polishings and other substances rich in "vitamines." Some of the reports of the results of this method of treatment have been overly enthusiastic, but definite progress has been made and a sound foundation for further investigation established.

The extremely grave and widespread infantile type of beriberi (taon and many other local names), as well as the multiple neuritis of pregnant and parturient women, constitutes one of the most interesting and baffling problems in tropical neuritis, which may have consideration in a subsequent article.

---

### CLINICAL DIFFERENTIATION OF EPIDEMIC ENCEPHALITIS, ACUTE POLIOMYELITIS, BOTULISM AND CERTAIN FORMS OF FOOD AND DRUG POISONING.

BY GEORGE E. EBRIGHT, M.D.

SAN FRANCISCO, CAL.

EPIDEMIC encephalitis, botulism, certain forms of acute poliomyelitis and cerebrospinal syphilis, wood-alcohol poisoning and poisoning by drugs, such as veronal and members of the belladonna group present in common involvement of the cranial nerves resulting frequently in considerable diagnostic difficulty. It is the purpose of this paper to present a comparison of the various points which may be used in differential diagnosis of these conditions.

**Poliomyelitis** (Acute Poliomyelitis, Polioencephalitis, Infantile Paralysis or Heine-Medin's Disease) was first described by Jörg in 1816, who noted the occurrence of a febrile disease followed by paralysis of the limbs and subsequent club-foot. It is hardly necessary at the present moment to review the contributions to the subject of Heine-Medin, Wickman, Peabody, Draper and Dochez, Flexner and Amoss, Webster, Rosenow and many others more than to say that the old conception of the disease as expressed in the term "infantile paralysis" has given way to the recognition of the fact that the disease is a general infection in which paralysis may or may not occur. It is characterized upon an average by an incubation period of variable duration, usually about a week, followed by a stage of prodromal symptoms which are at times slight and of a very transitory nature and easily overlooked, then an acute stage with paralytic manifestations and lastly a period of retrogression. The prodromal symptoms are of a very general nature and vary from epidemic to epidemic. They may be so

slight as to be entirely overlooked, and the first indication of the presence of the disease is then a paralysis. Undoubtedly the most constant and important symptom of this period is fever of an irregular character varying from a slight rise to 103° F. or more. Initial chills are infrequent. Profuse sweating has been noted by Müller in 75 per cent of his cases; other observers failed to notice any sweating in more than 25 per cent. It is evident that this symptom varies considerably. Drowsiness of varying duration and intensity may be present; the patient, however, may be easily aroused, but is usually found to be then irritable to a considerable degree. This irritability manifests itself in an expression of fear of being moved or examined, and is associated with another cardinal symptom, hyperesthesia of the skin and pain on passive motion, specially those motions which cause anterior flexion of the spine—or the legs at the hip-joint and forward bending of the neck. While retraction of the head is not often seen, there is, nevertheless, a tendency of the head to fall back when the child is lifted from the bed by the hands, and there may be found a stiffness of the posterior neck muscles. Test for Kernig's sign results in pain and resistance of the hamstring muscles. These pains and stiffened muscles are a result of meningeal irritation which occurs in the preparalytic stage. Before paralysis takes place there may also be a definite weakness of various groups of muscles, as seen in walking or standing. While convulsions are quite unusual, muscular twitchings are rather frequently seen.

The onset of the disease may be manifested by involvement of the respiratory tract as seen in an inflammatory reaction of the conjunctiva, nose, throat, bronchi or lungs. Regan describes at length the mouth and throat findings in his series of cases, and calls attention to congestion of the throat as an almost constant symptom in the early acute stage accompanied by a varying degree of capillary enlargement on the faucial mucosa and pharynx. The palate, pillars and uvula are a diffused deep red, the soft palate a deep red with distinct purple or violaceous tinge; the hard palate pink—the more severe the deeper the color. In the severe bulbar types in which the prognosis is bad there may be an anemic appearance of the throat. A mild tonsillitis he finds constant. There is never a membrane but spots similar to Koplik's spots sometimes are seen. The tongue is heavily covered with a grayish or white coating, usually moist, and the tip and edges uncovered and slightly redder than normal. The covering is absent in some places, so that the red shows through. The five most important signs of meningeal invasion are: Neck stiffness with weakness of the anterior neck muscles; unwonted drowsiness; hyperesthesia; ataxic gait and sometimes muscle twitchings. The first two combined are almost pathognomonic. In the bulbar type the child may be extraordinarily acute or stuporous. Constipation is

usually present and also anorexia. Urinary retention may occur during the fever; diarrhea with green mucous stools may be a predominating feature. Vasomotor disturbances, such as flushing of one ear or cheek, may occur. The spinal fluid usually is abnormal—it may be clear or slightly opalescent, under increased pressure, increased cell content and increased protein. If the clinical picture be considered with the spinal-fluid findings it may be possible to make a diagnosis in the prodromal stage. When paralysis occurs the diagnosis offers less difficulty.

*Paralytic Stage.* The paralysis may be considered from an anatomic point of view as follows: Spinal paralysis; paralysis of the diaphragm; paralysis of the intercostal muscles; paralysis of the abdominal muscles; paralysis of the neck and back muscles; bulbosplinal paralysis and rapidly progressive fatal cases presenting the symptom-complex of Landry's ascending paralysis, in which death ensues from paralysis of the respiratory organs.

The spinal paralyses present no special difficulty in diagnosis; in the great majority of cases muscles of one or both legs are paralyzed and in nearly one-half of the cases the paralysis is limited to the legs. Owing to the fact that the phrenic nerve has a large number of roots originating from the 3d, 4th and 5th cervical segments, paralysis of the diaphragm is comparatively rare, although in fatal cases it is usually present, being preceded, however, by paralysis of the intercostal muscles. Paralysis of the abdominal muscles may take place and is usually difficult of recognition. It is necessary to remember that paralysis of the neck and back muscles may occur. In the former it is impossible for a patient to support the head, which falls helplessly in one direction or another. While this condition may resemble the paralysis seen in botulism, the differentiation, as a rule, presents no difficulties, as in cases of poliomyelitis in which there is paralysis of the neck and back. There is generally, also, extensive paralysis of both arms and legs. The same may be said of most instances of combined spinal and bulbar paralysis which are associated with extensive lesions involving the arms and legs as well as the muscles supplied from the medulla. However, bulbar paralysis may occur without the association of spinal paralysis. The facial nerve is the one most often affected either in whole or in part. Palsies of the ocular muscles, specially the abducens, have been noted, sometimes extensive involvement of the eye muscles and even ophthalmoplegia externa; nystagmus is rare; involvement of the optic nerve practically never occurs; phonation and speech may be interfered with and swallowing is sometimes difficult. The tongue may be protruded to one side, or there may be bilateral involvement with inability to protrude the tongue at all. When bulbar paralyses occur in conjunction with spinal paralyses they are much less apt to be severe or lasting than when they occur alone. Associated with

these high lesions is an ataxia of the arms and legs with exaggeration of the knee-jerks and Achilles reflexes and a tendency to stiffness of the legs. Romberg's sign may be markedly present. While the exaggeration of the reflexes may be persistent for a long time the ataxia rapidly disappears.

In the rapidly progressive fatal cases the picture of an ascending paralysis is presented. The mind is usually clear and the patient dies when the diaphragm and the intercostal muscles become involved. Just as the occurrence of paralysis of an arm or leg may be a very sudden manifestation, so also may a sufficient paralysis to cause death occur in a very short time, sometimes within five hours. Ordinarily, however, there is at first a more or less extensive paralysis which involves either the diaphragm or the intercostal muscles followed by an interval of several days, then a slow extension of the paralysis until respiration finally ceases. Fever is always present in the fatal cases, ranging, as a rule, from 101.5° F. to 102.5° F., and sometimes not over 100° F. This occurrence of fever with the onset of the disease is in sharp contradistinction to the subnormal temperature which occurs in the early stages of botulism, fever not being present until a complication such as bronchopneumonia sets in. In both of these conditions, however, the mind is remarkably clear, differing from that seen in encephalitis lethargica. In the bulbar paralyzes of poliomyelitis the mouth secretions are not diminished as in botulism, and a frothy saliva fills the mouth and collects between the lips, while in botulism the salivary secretion is diminished, as are all other secretions, and a thick viscid mucous difficult of expulsion fills the throat.

*Cerebral Type.* Strümpell, in 1885, suggested the name polio-encephalitis for a group of cases of cerebral paralysis in children, and pointed out the resemblance to poliomyelitis. The onset of the disease was sudden with a febrile initial phase, vomiting, convulsions and prodromal period, sometimes absent, lasting for two or three days, sometimes over a week, marked by rapid convulsive seizures; after this time the child was found to have a hemiplegia which gradually began to improve. The paralysis was of the upper segment type without atrophy or reaction of degeneration and with exaggerated reflexes. There remained afterward in some of his cases permanent disturbances of cerebral function such as athetosis, epileptic seizures, speech disturbances and diminution of intelligence. He pointed out that, as in poliomyelitis, the lesion was in the gray matter of the cerebrum, the cortex. The final proof that typical cerebral paralyzes have the same etiology as poliomyelitis, in which the transference of the virus to monkeys and the causing in them of poliomyelitis has not been accomplished, but both a flaccid and a spastic paralysis have been found in the same patient and a flaccid paralysis in one member

of a family and a spastic paralysis in other members of the same family.

*Abortive Types.* This is the term applied by Wickman to those cases which show the usual prodromal or preparalytic symptoms, but which do not develop paralysis. These may be cases which run the course of a general infection in which meningeal irritation is specially marked or in which pain is a very marked feature, as in influenza or cases with predominating gastrointestinal disturbances. The serum of these patients acts in the same way that the serum of those who develop paralysis does. It neutralizes the virus *in vitro*, and it is interesting to observe that the serum of a patient who had been paralyzed thirty years before was still able to protect a monkey from the virus of poliomyelitis. Peabody, Draper and Dochcz in their monograph point out that it is quite probable that in the past many of the abortive cases have been unrecognized, and in some cases at least the apparent immunity of adults may be due to some previous unrecognized attack.

*Epidemic Encephalitis.* Epidemic encephalitis, like acute poliomyelitis, is a contagious disease due to a filtrable virus that exists in the nasopharyngeal secretion and in which the nasopharynx serves as a portal of acquisition and dissemination of the disease. While the virus may be preserved for a long period of time in glycerin its virulence is diminished by drying, and while undoubtedly it is usually a droplet-borne disease and propagated directly by the exhalations of the mouth from one person to another, it is, nevertheless, possible that the disease may be carried by insects, such as flies, as is also true of poliomyelitis. Like poliomyelitis also the possibility of convalescent or immune carriers must be considered as a possible and a probable source of the disease. The pathology consists typically of microscopic perivascular lymphocytic infiltrations scattered through the basal ganglia and particularly marked in the brainstem; small hemorrhages may occur, while visceral manifestations have been observed, such as enlargement of the spleen and mesenteric glands and ecchymoses in the pleura, pericardium, bladder and stomach. Visceral changes at autopsy are very inconstant. The blood examination shows nothing characteristic, although a moderate leukocytosis is the rule. The spinal fluid shows little or no change, the fluid is clear; the pressure is not increased; there may or may not be a slight increase of cells (lymphocytes); globulin is usually increased; Lange's colloidal gold test varies. According to Moffitt it may be entirely negative, quite frequently moderately luetic and more rarely an outspoken parctic one. He remarked that the Wassermann reaction is uniformly negative except in complicating cerebrospinal syphilis.

A characteristic feature of epidemic encephalitis is the spread-out course of the occurrence of the symptoms. This is in sharp



contradistinction to the rule in poliomyelitis, in which the entire extent of the paralysis may be accomplished in a few hours or at most in a few days. In one of my cases after an abrupt onset in which there was sudden double vision, gastric disturbances, horizontal and vertical nystagmus, unilateral ptosis, optic neuritis, inability to stand, lasting an hour or two, the patient improved during the course of a week, when a renewal of the symptoms occurred with paralysis of the facial nerve that in its turn disappeared in six or eight days, when suddenly an involvement of the hypoglossal took place with marked deviation of the tongue. One of Moffitt's cases died thirteen months after the onset from a relapse of the same type of the disease she had had at first. Others of his died from twelve days to seven weeks after the onset.

If one remembers the typical lesions of epidemic encephalitis, the small areas of lymphocytic infiltration lying about the blood-vessels and that they may occur in any part of the nervous system, he may more readily understand the varying combinations of symptoms, and if it be assumed that the virus of the disease is active within the patient for a varying period of time, sometimes for many weeks, the cause of the peculiar progression of the occurrence of symptoms will be evident.

If two or more of the cardinal symptoms of the disease occur—that is, a state of lethargy or somnolence, marked asthenia, fever of irregular type and cranial nerve palsies—epidemic encephalitis should be suspected. The suspicion is strengthened if the condition has been preceded by influenza. Fever may be slight and be entirely overlooked. The palsies most frequently involve the ocular muscles; there may be ptosis, more or less complete, strabismus, lateral and vertical nystagmus, pupillary changes, occasionally optic neuritis, all of which may be either unilateral or bilateral. Facial palsies occur, sometimes involving a muscle or small group of muscles, sometimes giving a Parkinsonian mask-like expression to the entire face. Pain, myoclonus and convulsions may occur and meningeal symptoms have been noted as dominating the picture. The pains may be of extreme severity, sharp, localized and extremely intractable; these pains may occur in any part of the body, as a finger, ear, in the abdomen, the teeth, the eye or elsewhere. They frequently precede myoclonus and usually stop when the myoclonic jerking of the muscles begins. Convulsions due undoubtedly to cortical irritation may be the initial symptom or may occur later in the disease. In mild cases somnolence may not be very marked, but, as a rule, lethargy distinguishes it from the mental condition of poliomyelitis or botulism. A varying degree of optic neuritis further distinguishes it from these two conditions.

**Botulism.** Botulism is a state of intoxication which follows the ingestion of the toxins produced by *Bacillus botulinus*, either

type A or B. It can be mistaken for methanol poisoning, epidemic encephalitis and cerebrospinal syphilis. Its symptoms usually occur from twelve to twenty-four hours after eating food containing the botulinus toxin, and may be preceded by gastrointestinal disturbances, particularly in the more severe and fatal cases. Symptoms may occur as early as two hours after or may be delayed for two or three days or even longer in making their appearance. One case has been reported nine days after and another as late as fourteen days, but these are indeed unusual.

The symptoms are classified as follows:

1. Arrest of secretions or hypersecretions of saliva and mucous secretions of the mouth and pharynx.

2. Ophthalmoplegia, externa and interna, more or less complete (blepharoptosis, mydriasis paralysis of accommodation, diplopia, strabismus).

3. Dysphagia, aphonia and rebellious constipation, urinary retention.

4. General weakness of all voluntary muscles.

5. Absence of fever and disturbance of sensation and absence of impairment of intelligence.

6. Respiratory difficulties and circulatory troubles, which frequently result fatally more or less rapidly from bulbar paralysis. There is more or less incoördination of muscular movements of the arms and legs, difficulty in picking up small objects, ataxic gait, usually no abnormalities of tendon reflexes.

The patient complains chiefly of double vision, of weakness, of difficulty in walking. There is pronounced difficulty in swallowing and in the expulsion of the thick, viscid, glairy mucus which accumulates in the throat. Agonizing strangling spells resulting in marked cyanosis are of frequent occurrence and often cause death, due to involvement of the respiratory muscles, either intercostals or the diaphragm, or both. There may be a sensation of great weight or pain in the chest and marked difficulty in breathing. The constipation is due to paralysis of the muscles of the wall of the intestines and may resist all efforts to overcome it for quite a number of days. The diagnosis, especially in sporadic cases, may be a matter of considerable difficulty. It may be confused with acute poliomyelitis, but there is an absence of prodromal symptoms, absence of fever, and in by far the greater number of instances of poliomyelitis there occurs definite paralysis of groups of muscles in the extremities. The posterior muscles of the neck in botulism, or indeed all of the muscles of the neck, may be paralyzed, so that the head has a tendency to fall forward. The patient frequently uses his hands to move his head. In poliomyelitis there is a stiffness of the muscles of the back of the neck and a weakness of the anterior muscles, with a tendency for the head to fall backward. There is also a varying degree of

pain on movement in poliomyelitis. In poliomyelitis the mouth secretions are not diminished. The pupils are widely dilated in botulism.

In differentiating botulism from cerebral spinal syphilis the difficulties may be very great, but manifestations of the latter are so generally well known that it is not deemed necessary to more than call attention to the resemblance of the two conditions.

Poisoning by drugs of the belladonna group (belladonna, stramonium, hyoseyamus) show inhibition of secretions and dilation of pupils as occurs in botulism. In belladonna poisoning mild cerebral symptoms regularly occur. The face and neck are flushed either uniformly or in blotches; there is an erythematous eruption of the throat and sometimes generally over the skin resembling that in scarlet fever; the respirations are rapid and deep; the arterial pressure is above normal and the patients pass into a chattering delirium with confusion or even into a maniacal condition; there may be a rise of several degrees of fever. Concentrated urine dropped into a cat's eye will dilate the pupil. In the final stages the heart fails, the blood-pressure is low and death takes place from failure of respiration.

Curare, a South American arrow poison, produces death by respiratory paralysis, as does also conium or poison hemlock. Socrates noted while dying of this poison that there was a paralysis with slight numbness beginning in the toes and gradually ascending until it involved the trunk. Gelsemium acts peripherally like conium, but is more depressing centrally. It has an atropine-like action on the pupil and accommodation.

*Veronal Poisoning.* I have seen two patients undoubtedly suffering from veronal poisoning, one of which resembled encephalitis. She showed after the ingesting of 105 grains of veronal over a course of four days marked double ptosis, double vision, pronounced lateral nystagmus (except when the eyes were at rest), negative pupils, normal reaction to light and distance, no paralysis of cranial or other nerves, no retinal changes, no gastrointestinal disturbance, no diminution of secretion.

*Methanol or Wood Alcohol Poisoning.* Since the advent of prohibition there has arisen a formidable mass of literature upon this subject. In acute methanol poisoning there occurs: (1) Unconsciousness terminating either in death or recovery of mentality before twenty-four to forty-eight hours; (2) cyanosis; (3) pupils equal and enlarged, sometimes widely dilated with sluggish reaction to light; (4) respirations slower than normal, ten to twenty per minute; temperature, 98.6° to 100° F. Chemical analysis of early catheterized urine may show presence of formaldehyde; the stomach content may contain methanol. The most striking evidence of this poisoning is blindness, due to optic neuritis fol-

lowed by atrophy, which has been known to occur after the ingestion of so small a quantity as a teaspoonful or two.

Acute methanol poisoning may present: (1) A mild intoxication with some dizziness, nausea and mild gastrointestinal disturbance followed in a few days by recovery, but occasionally resulting in more or less serious damage to vision; (2) more pronounced effect with marked dizziness, outstanding persistent nausea, more or less severe gastroenteritis, dimness of vision frequently increasing to blindness; (3) overwhelming prostration with coma and death. The patient invariably dies in an unconscious condition, or having regained consciousness suffers relapse and death follows shortly. Generally will be witnessed in severe methanol poisoning what appears to be the ordinary effects of alcoholism—vertigo, nausea, cloudiness of mental functions, exaltation of ideas, general malaise, muscular incoördination and disturbance of vision; blindness may take place very suddenly. The condition of the optic nerve and the mental condition should clearly differentiate it from botulism and poliomyelitis.

Poison from decomposed fish and shell fish bears resemblance to botulism, but the symptoms of poisoning follow more quickly after ingestion of food, is marked by predominating gastrointestinal disturbances and the well-known skin manifestations, specially urticaria.

Conclusive proof of the diagnosis of botulism rests in the recognition of the presence of the toxin of bacillus botulinus or the discovery of the organism itself, which is always present in the contaminated food. The suspicious food and the containers of it should be carefully searched for and subjected to bacteriologic tests such as described by Meyer. Inasmuch as the toxin of type A, which commonly gives trouble in the United States, is poisonous to chickens, Graham has suggested the feeding of suspected material to chickens, which will show characteristic manifestations of botulism. It should be remembered that the ingested food may remain for many days in the stomach and in the intestines of the patient. This fact should be taken advantage of in examining the intestinal content of the patient as well as the stomach content for bacillus botulinus and for its toxin.

#### REFERENCES.

Regan: Skin and Throat Manifestations of Heine-Medin's Disease, Arch. Ped., 24, 884.

Howe: Contributions to the Study of the Pathology of Human and Experimental Pathology Based on Cases Occurring in the Epidemic of 1916 in New York City, Jour. Nerv. and Mental Dis., 48, 97-206.

Armstrong: Early Manifestations and Diagnosis in Poliomyelitis, Illinois Med. Jour., 33, 11.

Webster: Poliomyelitis: Pathologic Notes and Experimental Study, Med. Jour. of Australia, 1, 19.

- Abrahamson: Pathologic Report on Forty-three Cases of Acute Poliomyelitis, *Arch. Int. Med.*, 22, 313.
- Flexner, Simon and Amoss: Localization of the Virus, Pathogenesis of Epidemic Poliomyelitis, *Jour. Exp. Med.*, 20, 249.
- Pratt: Differential Diagnosis between Anterior Poliomyelitis, Epidemic Cerebrospinal Meningitis and Tubercular Meningitis, *Minnesota Medicine*, 1, 224.
- Larkin, Cornwall: Some Observations of the Spinal Fluid in Anterior Poliomyelitis, *Arch. Ped.*, 35, 459.
- Regan: A Consideration of the Complications of Poliomyelitis and of the General Treatment of the Acute Stage, *Arch. Ped.*, 35, 257.
- Rosenow: Treatment of Acute Poliomyelitis with Immune Horse Serum and Summary of Results, *Jour. Am. Med. Assn.*, 77, 8.
- Tumpowsky: Symptoms, Diagnosis and Treatment of Acute Poliomyelitis, *Illinois Med. Jour.*, 33, 218.
- Peabody, Draper and Doebe: A Clinical Study of Acute Poliomyelitis, Monograph No. 4, of Rockefeller Institute for Medical Research, June 1, 1912.
- Meyer: Some Suggestions Concerning the Bacterial Diagnosis of Human Botulism, *U. S. P. H. Reports*, 36, 23.
- Meyer and Geiger: The Distribution of the Spores of *Bacillus botulinus* in Nature, *U. S. P. H. Reports*, 36, 4.
- Geiger: An Outbreak of Botulism at St. Anthony's Hospital, Oakland, Cal., in October, 1920, *U. S. P. H. Reports*, 35, 2858.
- McCasky: *Bacillus Botulinus* Poisoning with a Report of Seven Cases, Four of Which Proved Fatal, *Am. Jour. Med. Sc.*, 157, 57.
- Randell: Botulism from Canned Beets, *Jour. Am. Med. Assn.*, 75, 33.
- Siseo: An Outbreak of Botulism, *Jour. Am. Med. Assn.*, 74, 516.
- Dickson and Howitt: Botulism: Preliminary of a Study of the Antitoxin of *Bacillus botulinus*, *Jour. Am. Med. Assn.*, 74, 718.
- Dickson: Botulism: A Clinical and Experimental Study; Monograph No. 8, Rockefeller Institute for Medical Research.
- Dickson: Botulism: *California State Jour. Med.*, 18, 40.
- Graham and Schwarze: Avian Botulism (Type A or Limber Neck), *Jour. Infect. Dis.*, 28, 317.
- Weiss: The Heat Resistance of Spores, with Special Reference to the Spores of *Bacillus Botulinus*, *Jour. Infect. Dis.*, 28, 70.
- Bennington: Standardization of Botulism Antitoxins, *Am. Jour. Pub. Health*, 11, 352.
- Orr: Study of *Bacillus botulinus*, *Jour. Med. Research*, 42, 127.
- Graham and Schwarze: Botulism in Cattle, *Jour. Bact.*, 6, 69.
- Graham and Bruckner: Study in Forage Poisoning, *Jour. Bact.*, 4, 1.
- Burke: Notes on *Bacillus Botulinus*, *Ibid.*, p. 555.
- Edmondson, Giltner and Thom: The Possible Pathogenicity of *Bacillus Botulinus*, *Arch. Int. Med.*, 26, 357.
- Glancy: Botulism: A Clinical Study of an Outbreak in the Yukon, *Canadian Med. Jour.*, 10, 1027.
- Graham and Schwarze: Differentiation of Type A and Type B in Botulism Toxin in Food: Rapid and Simple Method, *Jour. Am. Med. Assn.*, 76, 1742.
- Hubbard: Wood Alcohol Poisoning, *New York Med. Jour.*, 3, 16.
- Baskerville: Some Chemical Aspects of the Wood Alcohol Problem, *New York Med. Jour.*, 3, 580.
- Norris: The Lesions in Wood Alcohol Poisoning, *Ibid.*, 583.
- Cutler: Wood Alcohol and the Eyes, *Ibid.*, 585.
- Corora: Wood Alcohol Poisoning, *Ibid.*, 588.
- Gettler and St. George: Wood Alcohol Poisoning, *Jour. Am. Med. Assn.*, 70, 145.
- Harrop and Benedict: Acute Methyl Alcohol Poisoning Associated with Acidosis, *Jour. Am. Med. Assn.*, 74, 25.
- Betts: Four Cases of Wood Alcohol Poisoning from Drinking Bay Rum, *U. S. Naval Med. Bull.*, 13, 791.
- Gaines: A Consideration of the Clinical Features of Epidemic Encephalitis, *Southern Med. Jour.*, 14, 381.
- Moffitt: Epidemic Encephalitis, *California State Jour. Med.*, 19, 305.
- Burke: The Occurrence of *Bacillus Botulinus* in Nature, *Jour. Bact.*, 4, 542.

## THE STATUS OF EXERCISE IN THE TUBERCULOUS CONSIDERED FROM A NEURO-MUSCULAR VIEWPOINT.

BY FRANK PORTER MILLER, M.D.,

LOS ANGELES, CAL.

It is the purpose of this paper to record the more important mechanistic changes incident with physiologic exercise, and at the same time to parallel the maladjustments as they occur in the individual who is suffering from an active tuberculosis.

Muscular exercise should be considered from the standpoint of a neuro-muscular system, and we should ever bear in mind the continual adjustments which are occurring in the respiratory and circulatory mechanism. Exercise produces a subconscious concentration of energies of the higher nerve centers, and it is this expenditure which we must conserve. Furthermore, an improper conception of its character will be attained if it is considered as a purely muscular act. For a person to enjoy muscular exercise it is necessary that the movements of the skeletal muscles and those of the respiratory and circulatory system should be coördinated and integrated into a unit, as they are indissolubly linked together.

Exercise is purely an outward expression of neurogenic action, and when once it is initiated, the different processes then occur in sequential order until the action resembles a machine; and considered from this viewpoint it is not difficult to understand that inefficiency of any part of the mechanism would inevitably spell defeat.

A man's nervous organization is as important as his muscular development, and his ability for performing muscular work is not altogether gauged by the size of the musculature. As a rule the heart is the limiting factor which gauges exercise. Every voluntary movement adds to the work of the heart: (a) by increasing the output because the larger venous inflow; (b) the blood is expelled against a higher arterial pressure.

The source of muscular energy is to a large extent derived from carbohydrates and fats, and the belief that protein furnishes a portion of energy has long been abandoned. The conversion of potential into kinetic energy involves the liberation of lactic acid, which is an intermediary product of carbohydrate combustion. During the process of muscular exercise lactic acid is oxidized within the muscle, if the exercise is not too violent; in event that it is strenuous it then escapes into the blood stream.

It might be well at this point to introduce the method we employ in all cases of active disease. Every case is immediately placed in bed, the period of rest is variable, and not infrequently we find it necessary to confine cases to the prone position from eighteen

months to two years. All trays are served in bed, and the only exercise permissible is toilet exercise. If there is one single factor which has enhanced the results in the last few years it has been the proper appreciation of rest. It is our plan to carry rest to the nth power, and I am of the opinion that our results would be somewhat hastened if we insisted that the patient maintains the prone posture and not be allowed the laxity of sitting up in bed for long intervals.

From the foregoing remarks the influence of attitude may seem superfluous to the reader, but even a change of position from lying down to sitting or standing has a definite effect on both the consumption of oxygen and the pulse-rate. There is an approximate increase in the pulse-rate of 25 per cent and an increase in oxygen consumption of 20 per cent. This can be explained on the assumption that a greater number of impulses are coursing from the cerebral cortex to the bulb, or, in other words, utilizing the same mechanism brought into action as that occurring at the outset of exercise. Furthermore, very little energy is necessary when lying down, but if allowed to walk it requires 100 per cent more expenditure.

At the outset of exercise impulses pass from the higher centers, and probably mainly from the motor area of the cerebral cortex to the medulla. The irradiation of impulses which occur stimulates the vasomotor, respiratory and cardio-inhibitory center, raising blood-pressure and increasing pulse-rate and respiration. Simultaneous with this impulses are sent to the skeletal musculature via the pyramidal tracts and down the cord through the lateral splanchnic motor-cell columns to the V-XII thoracic segments, producing a constriction of the splanchnic area. With a contraction of the skeletal muscles and a forcing of the blood from the splanchnic area there is an increased venous pressure, and also the diastolic volume of the heart is greatly increased. When once exercise is thoroughly instituted the muscles squeeze the blood from the smaller capillaries into the larger veins and in this manner act as a subsidiary pump.

Coincident with muscular contraction lactic and carbonic acids are formed, also acid metabolites. It seems that in almost every type of exercise the oxygen supply is inadequate for complete oxidation, and particularly lactic acid makes its entrance into the blood stream, which immediately affects the hydrogen-ion concentration of the blood. There is an equilibrating force which now comes into action and the "buffer substances" or alkali reserve of the blood attempts to equalize the condition—that is, the lactic acid reacts with the plasma bicarbonate forming carbonic acid. Carbonic acid in solution acts as an acid, and this produces an increased pulmonary ventilation by its action upon the respiratory center. By increasing the pulmonary ventilation additional work is thrown upon the heart, as the output of the heart is directly proportional to the consumption of oxygen.

It is our observation in tuberculosis that a high-grade toxemia may exist without the presence of temperature. Toxemia in itself changes the chemical composition of the blood by raising hydrogen-ions, and this favors necrosis of tissue. Exercise in the individual actively tuberculous plus a moderate grade of toxemia can attain but one end, and that is tissue-destruction.

I am of the opinion that healing is greatly facilitated when the hydrogen-ion concentration of the blood remains as nearly as possible at a normal level. It is a notorious fact that a portion of the healing which occurs in tuberculosis is due to the deposition of lime salts; especially is this true if there have been areas of caseation. If some condition, such as exercise, is superimposed upon this preëxisting condition, then the reaction of the tissues swing toward the acid side, with a depletion of "buffer substances" in the blood. Hence the healing is delayed, as it is dependent in a measure upon the alkaline salts.

Bradley and Taylor<sup>1</sup> have put forward the view that the hydrogen-ion concentration within the tissues is an important factor in the building up or breaking down of tissues, as the case may be. They have adduced evidence that when the reaction of the blood swings toward the acid side reserve protein is transformed into "available protein," and this undergoes autolysis. They are of the opinion that a greater blood supply and a more complete removal of acid products may reverse the process and lead to a laying down of reserve protein and, therefore, to growth of the cell. This view is very suggestive that the tissues are quite susceptible to the medium in which their activities are carried on. It is quite plausible that a shifting in the point of equilibrium would bring about autolysis on the one hand and a synthesis of tissue on the other.

In the early phase of exercise the higher centers are utilized to great advantage, but later these changes are produced by chemical means. The hydrogen-ion not only acts upon the respiratory center but it also lessens the tone of the arterioles and capillaries and maintains an adequate supply of oxygen to the part. Furthermore, it accelerates the dissociation of oxyhemoglobin to the muscles and acts upon the vasomotor center.

Maladjustments of the cardio-respiratory mechanism produce interesting symptoms. Practically every symptom which occurs is explainable either upon a mechanic or neurogenic basis. One of the dominant features evidenced by ill-advised exercise is the rapidity of the heart, and frequently the patient becomes extremely cautious because of the palpitation. It is fair to assume in any chronic disease in which there is wasting of musculature that the nutritive condition of the heart must also suffer. In many cases of tuberculosis the heart has undergone a physiologic atrophy, due to

<sup>1</sup> Studies on Autolysis, III. The Effect of Reaction on Liver Autolysis, Jour. Biol. Chem., 25, 261.



a lessened venous inflow. Primarily this is caused by costal inspiration, which lowers arterial pressure. As a sequel to the above we would expect a loss of contractile power of the heart, and such does occur, due to ventricular thinning. When exercise is instituted in these individuals the mechanical pumping action of the peripheral muscles squeeze the blood from the smaller vessels into the great veins, raising venous pressure and increasing the diastolic volume of the heart. The heart now dilates to its physiologic limits, but with some loss of contractile power it is unable to empty itself at the end of systole. To maintain the minute volume it is necessary that compensation occur, and this is effected by an acceleration of the pulse-rate or palpitation.

The early coördinating mechanism of exercise sends impulses via the descending tracts in the cord to the stellate ganglion, thus activating cardiac musculature and also to the vagal center producing a lessened tone. There are many cases, especially the incipient type, in which the palpitation is purely neurogenic. Furthermore, it is well to bear in mind the effects of costal inspiration and its relation to arterial pressure. It is not an uncommon occurrence in our cases for the pressure to drop below 100 mm. Hg and frequently below 90 mm. Markwalder and Starling<sup>2</sup> have shown that the coronary circulation is dependent upon the tone of the coronary vessels, but to a greater extent upon arterial pressure, and in the event that the pressure falls below 90 mm. Hg the blood supply is inadequate for the nutrition of the heart. The type of case which is most liable to show this is one in which fibrosis is extensive, and there is an associated pleuritis from apices to base. The heart being unable to adjust itself to this environment will attempt compensation and dilatation follows, which is the closing act in practically all forms of pulmonary tuberculosis.

Rise in body temperature during exercise is dependent upon the severity of the exercise. It is not uncommon to record a physiologic rise of 102°F. Loss of heat is dependent upon the outside temperature, humidity, presence or absence of winds and the nature of clothing worn. Dissipation is hastened in the patient who is lean and sparse, but a great deal slower in one possessing a large amount of subcutaneous tissue. Rise in the temperature of the body heightens the excitability of the nervous system and hastens metabolism. Physiologic rise involves carbohydrate and fat oxidation while a pathologic elevation produces protein destruction. Recent metabolic findings have shown that protein oxidation is not as great as we were formerly taught.

As impulses leave the cerebral cortex there is a wide distribution both supra- and infrasegmentally, and while a great many spend their momentum upon volitional control, an equal number activate

<sup>2</sup> A Note on Some Factors Which Determine the Blood Flow Through the Coronary Circulation, *Jour. Physiol.*, 47, 275.

those structures supplied by the vegetative system. During this dissemination stimuli are sent to the central sympathetic apparatus (Edinger) located in the midbrain and then migrate down the lateral splanchnic column, stimulating motor cells of sympathetic division and thereby producing a peripheral vasoconstriction and lessened dissipation of heat. Any impulse reaching the tuber cinereum, corpus striatum or any of the subsidiary thermogenic centers would produce a like result.

Those endocrine structures receiving a similar nerve supply become activated to a greater extent, and this probably accounts for the increased metabolism. Furthermore, the destruction of any foreign protein paraenterally shows a predilection for this particular division of the nervous system. Temperature should be considered as a beneficial phenomenon, and is simply the war that is being waged between the tubercle bacilli and the specific proteolytic enzymes generated by the tissues, and only by this procedure can organisms be annihilated. No longer should it be considered as a distinct entity, and we should bear in mind the numerous extraneous factors which may either cause elevation or depression, and remembering that toxemia is only one cause which provokes pyrexia. There are a great number of individuals who are distinctly sympathicotonic, and temperature in their respective cases is of least import.

When the activity within the lung has become quiescent the patient is then allowed to sit up, beginning with ten minutes each day and increasing ten minutes until they are sitting up either three or four hours. Exercise is then instituted, and the type most frequently resorted to is walking. Why should walking be given the preference over other forms of exercise? We unconsciously attempt to prescribe some form of exercise which is the most economic from the viewpoint of nerve expenditure. Every individual is trained in walking, and by utilizing this fact they receive the optimal benefit, and at the same time we are conserving the nervous system. Useless and ineffective movements are eliminated when we prescribe an exercise with which the patient is accustomed.

Every case should be individualized relative to exercise and never force walking to the point of fatigue. In the event that the patients complain of tiring no additional exercise should be indulged in until they are able to carry out their prescribed distance with comfort. The causation of the sensation of fatigue is rather obscure. Mosso long ago stated that "nervous fatigue is the preponderating phenomenon and muscular fatigue also is at the bottom an exhaustion of the nervous system." There appear, however, to be two types of fatigue: one arising entirely within the central nervous system and the other in which fatigue of the muscles is superadded to that of the nervous system.

It has been suggested that fatigue may be produced by exhaustion

of the store of energy within the muscle and the clogging of the muscular machine by the metabolic products. During exercise the steady outflow of impulses to the muscles, the complex neural processes involved in any voluntary movement and the focussing of the attention upon the exercise must involve considerable expenditure. Hence it is easy to see that fatigue could be induced with very little exercise unless the walking is carefully gauged.

I have attempted to visualize exercise from a different phase than it is usually attacked and to appreciate the significance of the various symptom-complexes which may be produced in consequence of a pathologic process affecting the lungs.

---

## POSTOPERATIVE MASSIVE COLLAPSE OF THE LUNGS.

By F. J. HIRSCHBOECK, M.D.,

THE DULUTH CLINIC, DULUTH, MINN.

RATHER singularly the subject of massive collapse of the lungs as a postoperative complication has scarcely been mentioned in American medical literature up to the present time, and only by English or Canadian authors. The importance of its consideration is accentuated by the fact that it undoubtedly occurs very commonly both in civil and military practice, and also because it is frequently confused with other more or less common postoperative pulmonary complications such as pneumonia, pleuritis, pleural effusions, etc.

Attention was first drawn to the occurrence of massive collapse of the lungs by W. Pasteur,<sup>1</sup> who cited 34 cases as occurring with postdiphtheritic paralysis of the diaphragm or other accessory respiratory muscles in 1890. It is interesting to note that Pearson-Irvine, in 1876, made the observation on cases which undoubtedly were cases of massive collapse, "That the physical changes observed in the lungs were the result of paralysis of the muscles concerned in the elevation and expansion of those parts." In a later series of 64 cases of postdiphtheritic phrenic paralysis, with 15 fatal results and with autopsies on 8 of these, Pasteur was able to demonstrate the gross pathology in 5, the others proving to be cases of bronchopneumonia. The cases were all bilateral, in a more or less advanced collapse, and all presenting the same characteristics *en gros*, the parts being entirely devoid of air, of a deep, definitely circumscribed blue color and sinking entirely in water. Pasteur noticed the similarity in the symptomatology between numerous clinical cases developing postoperatively and these cases of postdiphtheritic paralysis

<sup>1</sup> Internat. Jour. Med. Sc., 1890.

with collapse of the lungs. In 1908, in the Bradshaw lecture before the Royal College of Physicians, he drew attention to the condition, since which time he has encountered an increasing number of these cases and a corresponding diminution in those of postoperative pneumonia.<sup>2</sup> The clinical features were accurately described, the diagnosis elaborated, and in 1914<sup>3</sup> he published an article drawing attention to its frequency. Of 201 lung complications out of 3559 cases, in the Middlesex Hospital between 1906 and 1910, he found 12 cases of massive collapse, with 1 death; in frequency less than pneumonia, bronchitis or dry pleurisy, but more common than embolism, abscess or pleural effusion. It was found to occur with all methods of anesthesia, and occurred following operations on all areas of the abdomen.

About the same time Pasteur wrote his contribution in 1914, Dingley and Elliott<sup>3</sup> published an article in the *Lancet*, inspired by Sir Rickman Godlee, who showed them several cases encountered in his practice. During a period of two years the writers observed 11 cases, all of which followed abdominal operations. Their contributions to the literature is noteworthy chiefly on account of their consideration of the possible causes of this condition. They recalled Lichtheim's<sup>4</sup> observations, made in 1878, in which he had produced a condition similar, in rabbits by introducing laminaria plugs into the bronchi, resulting in a collapse of the lung tributary to the bronchus, which was the subject of the experiment. The alveoli were passively closed by absorption of the air content into the circulating blood, producing thereby a negative pressure, causing the neighboring organs to be dislocated. Dingley and Elliott conclude that in man, in addition to the comparative immobility of the thoracic wall, secretion blocks the smaller bronchioles, with the result that collapse ensues, just as in Lichtheim's animal experiments. Pasteur postulated an active collapse of the lungs, with an absence of any obstruction to the air passages, which he thought was induced by reflex inhibition of the diaphragm. He believed the collapse, to put it simply, to be due to alveolar expulsion rather than alveolar absorption.

Rose Bradford<sup>5</sup> devotes a chapter to the consideration of this subject in a recent *System of Medicine*, in which he refers largely to previous articles written by him in 1918-1919.<sup>6</sup> His experience was largely with military practice, with a large incidence, particularly in gunshot wounds of the chest, in which injuries he believes it occurs in 5 to 10 per cent of the cases. He points out that in gunshot wounds of the head or arms massive collapse has not been known to occur, but is occasionally seen as a complication in wounds of the

<sup>2</sup> British Jour. Surg., vol. 1.

<sup>3</sup> Lancet, London, May, 1914.

<sup>4</sup> Arch. f. exper. Path. u. Pharmacol., 10, 54.

<sup>5</sup> Oxford Loose-leaf Medicine.

<sup>6</sup> Quart. Jour. Med., 1918-1919.

buttocks, pelvis and thighs, assuming therefrom that the degree of immobilization is a factor in its production.

Briseoe,<sup>7</sup> in 1920, emphasized the effect of deficient respiratory excursion and a recumbent posture in causing diaphragmatic fixation with pleuritis, and coincidentally pulmonary deflation.

Recently, Seringer<sup>8</sup> in his article speculates on the various theories heretofore promulgated regarding the causation of massive collapse, and adds his belief that the lesion is probably due to an abdominal interference with the vagus control, causing a contraction of the muscular elements of the lung, aided by the subsequent collection of mucus in the bronchi sufficient to prevent the egress of air and leading to absorption of the alveolar air content and ultimately collapse. His article is interesting, particularly on account of the roentgenographic studies, which in some of his cases show most extravagant alterations in the relationship between the intrathoracic organs.

It is my belief that various factors may produce the lesion and that they are probably never entirely single, except in postdiphtheritic paralyses, in which the immobility of the diaphragm is so extreme as to be strikingly conclusive as to its being the cause. One must bear in mind that on the one hand Liehtheim's experiments are difficult to refute with his careful experimental technique, whereas on the other hand the evidence offered by postdiphtheritic phrenic paralysis is equally incontrovertible. There is no doubt that the recumbent position, as emphasized by Rose Bradford and Briseoe, is an important subsidiary factor as well as deficient aëration of the lungs. It is probable that in civil practice the incidence is more common in abdominal surgery, leading to more or less fixation of the diaphragm, due to a reflex inhibition, with an effort to cause a splinting action on account of the neighboring trauma. The theory that the recumbent posture is a factor is corroborated by the non-occurrence of massive collapse in injuries not requiring immobilization of the body such as injuries to the head and arms, as observed by Rose Bradford. The admonition to take deep breathing exercises systematically after operations would not only promote aëration of the more distal parts of the bronchial tree, but would also tend to reduce the immobility of the perithoracic musculature. I think it reasonable to assume that with the lack of mobility in the accessory muscles of respiration and the diaphragm, pulmonary expansion and retraction are necessarily limited. Mucus is formed and not expelled, causing an obstacle to the ingress of air into the smaller bronchioles, leading to ultimate alveolar absorption of the air into the circulation.

Bronchial obstruction, therefore, and muscular immobility tend to bring about this condition, one factor or the other predominating,

<sup>7</sup> Quart. Jour. Med., 1920.

<sup>8</sup> Surg., Gynec. and Obst., No. 6, 32.

however, in individual cases, leading to alveolar absorption, and finally the condition of massive collapse.

The extent and the site of involvement in massive collapse vary considerably. In most cases there is only a partial involvement of one of the lower lobes of the lungs; in others the condition is more extensive, involving a whole lobe or even an entire side. It is rather frequently bilateral. The noteworthy feature is the fact that in unilateral trauma collapse occurs not only on the side affected but oftentimes on the contralateral side, as was pointed out by Rose Bradford and others.

**Physical Signs and Symptoms.** The physical signs and symptoms of massive collapse are so distinctive that it is curious that the condition has not been recognized more commonly and described more frequently. A careful study of the case will make differentiation from conditions simulating it very easy. The exciting factor varies a great deal, and any trauma, either accidental or otherwise, necessitating more or less immobilization of the body may bring about the condition. It has been known to follow all methods of anesthesia, has occurred with local anesthesia and without any anesthesia at all. Aside from military practice I believe that in civil life it will be found that abdominal operation is the most frequent cause of the condition, on account of its immediate effect in requiring immobilization, producing immobility of the diaphragm and deficient aëration of the lungs. The condition may develop within a few hours or as late as one week after the exciting trauma. The onset is sudden, the course either rapid or at times protracted and resolution either prompt or slow. The degree of temperature is usually very moderate, but may be as high as 103° or 104°F, the coincidence of inflammatory phenomena probably influencing the height of the temperature curve. The respiration rate is increased by the immobility of the affected part, by an accompanying pleuritis or by toxie conditions incident to inflammatory complications. The pulse-rate is found to be more or less in direct relationship with the respiratory and thermic changes, but is less marked in uncomplicated cases, as would be naturally inferred.

On examining the chest one is impressed by the diminished or absent excursion of the chest wall over the affected area. The cardiac impulse is displaced toward the affected side and is as marked in the left-sided cases as in those occurring on the right side, the apex having a tendency to tilt outward and upward, so that the apex-beat may be felt in the axilla. In right-sided affections the impulse may be felt at the tip of the sternum or to the right of it. These signs are corroborated by roentgenographic study, the heart retraction being most marked, the dome of the diaphragm ascending to an unusual degree and the pulmonary area appearing partially or totally collapsed. In bilateral affections the displacement of the heart is absent, but the high position of the diaphragm and the

collapse of the lungs are easily manifest. On palpation the intercostal spaces on the affected side are found to be narrowed, leading to a relative approximation of the ribs. The percussion note over the affected area is dull and may approach flatness. Rose Bradford points out that in left-sided cases the lower part of the chest wall is highly resonant, due to the abnormally high level of the diaphragm, the liver interfering with this symptom in right-sided cases. Breath sounds and fremitus are usually increased, sometimes enormously so, but may be diminished or absent. The transmission of voice sounds may be so intense as to approach whispered pectoriloquy.

Bronchophony was present in all of my cases, and in no case was there diminution of the breath sounds or fremitus. No doubt the alteration in the transmission of sounds is due to the relative proximity of the affected area to sound-conducting bronchial tubules. Rales are usually absent in the early stages, but supervene as the case progresses, probably due to a bronchitis, resolution or an occasional pneumonia developing. In a great many cases a pleural friction rub is plainly audible. In the later stages of the condition, when expectoration is rather profuse and resolution occurs, rales are more frequent. As resolution occurs the heart gradually returns to its original position, the lungs slowly expand and the diaphragmatic dome flattens out.

The extent of the symptoms and the ease of recognition depend, of course, upon the amount of lung tissue involved and as to whether the condition is unilateral or bilateral. It is readily understood also that the influence of the condition on the patient's economy is dependent largely upon complicating factors as well as upon the extent of the lesion. Dyspnea may be moderate or extreme, as it usually is in bilateral cases. The cough is slight, as a rule, in the beginning, with a rather scant expectoration, but in the later stages it is accompanied by an expectoration of profuse mucopurulent sputum. My experience bears out the previous observation that the sputum is rarely or never bloody—an important consideration in the differentiation between pneumonia or infarct and collapse.

Bronchitis, pleurisy and pneumonia are recognized as complications. Effusion has been known to follow pleurisy. A differentiation must be made between pneumonia, hypostatic congestion of the lungs, embolus, infarct, pleuritis (with or without effusion), hemothorax and massive collapse. When one bears in mind the outstanding pathognomonic signs of massive collapse, confusion with other conditions is difficult. One must bear in mind that the affected side is retracted and does not expand with inspiration. The diaphragmatic and cardiac displacement is extreme and the general symptoms invariably less severe than with pneumonia or embolus. The very marked dullness, the extreme increase in the breath sounds (as usually noted), the scant expectoration, the comparative absence of constitutional signs in the non-occurrence of

complications, accompanied by displacement of the heart and diaphragm and roentgenographic studies, easily establish the diagnosis.

The prognosis is invariably good, but bilateral cases, or cases affecting more than one lobe, are more apt to be fatal, particularly in debilitated subjects.

A brief case report of the cases occurring in our practice is submitted, chiefly because of the interesting autopsy findings in the fatal case:

CASE I.—Mrs. D., aged thirty-eight years, was admitted to St. Mary's Hospital, Duluth, November 19, 1920. Her general condition was good.

She was operated upon November 20, by Dr. W. A. Caventry, for the removal of an ovarian cyst and appendix. The gall-bladder and stomach were examined and were found normal. Her temperature before operation was 98.6°F. and the leukocyte count 9000.

November 22 (two days after the operation) the pulse rose rapidly from 90 to 130 and the temperature to 101°F. The temperature and pulse varied little from this day until November 25, when there was a gradual reduction, day by day, until normal on November 28. The leukocyte count on November 22 was 21,200 and on November 25 it was 14,600.

*Physical Findings.* There was limitation of motion on breathing of the left side of the chest. There was marked dulness over the lower lobe of the left lung. Bronchial breathing was present over the area of dulness and no rales were heard. The left border of the heart extended nearly to the axillary line and the apex-beat was felt in the fifth interspace, 5 cm. outside the nipple.

There was no change the following day except that the bronchial breathing was further increased.

November 25, when the patient's condition was better, the left border of the heart had approached its normal position, the bronchial breathing had become vesicular and mucous rales were heard.

CASE II.—Mr. W., aged forty-nine years, was admitted to St. Mary's Hospital, Duluth, June 23, 1921, with an acute appendicitis. The temperature was 100°F. and the leukocyte count was 20,000.

He was operated on the same day, by Dr. T. L. Chapman. A gangrenous appendix was removed and was closed without drainage.

June 24, the day following the operation, his temperature rose to 102°F. and the pulse to 110. The patient was apparently distressed. Examination of the chest showed an area of dulness, approaching flatness, corresponding to the lower right lobe. Moderate bronchial breathing with increased transmission of whispered sounds. The left border of the heart was displaced to the right about 6 cm.



The following day the patient's condition was about the same, but the temperature had risen to 104°F. and the pulse to 120. The physical signs were the same. There was still an absence of any rales. In the evening of June 25 the temperature dropped to 99°F. and the pulse to 85; the patient was apparently much better.

The following morning the right lower chest was resonant, a few rales were heard and the heart approximately was in the normal position.

CASE III.—Mr. E. J. M., aged forty-eight years, was admitted to St. Mary's Hospital, Duluth, April 2, 1921, and was operated on April 6 for a chronic duodenal ulcer. An appendectomy and posterior gastroenterostomy were done.

April 8 the patient suddenly developed acute respiratory distress, with moderate cyanosis. The temperature at that time was 99°F. and the pulse was 110.

April 9 his temperature was 101°F.; pulse, 140; respiration, 38. Physical examination showed the patient to be in severe distress, with difficulty in breathing and in an apprehensive condition. The bases of both lungs expanded poorly. The vocal and tactile fremitus were increased on both sides. Dulness was extreme. On auscultation there was marked increase in the transmitted breath and whispered voice sounds. There was no displacement of the apex-beat. The patient's condition was too grave to permit of roentgenographic studies, became rapidly worse and he died on April 10.

A partial autopsy was permitted, consent being given to open the operative wound. This was found to show moderate healing and was void of any visible evidence of infection. The site of the gastroenterostomy and the appendicular stump were clean and without adhesions. It was necessary to deliver the lungs through the diaphragm, which was done without very much difficulty. The appearance of the lower lobes on both sides was most striking. Definitely circumscribed areas involved nearly the whole of both lower lobes, sharply demarcated from the normal tissues by a deep violet color. The collapsed areas were definitely depressed in relation to normal lung tissue, and contained no air, blood nor pus in the alveolar areas. The upper lobes were normal in appearance and showed no evidence of hypostatic congestion.

Cut sections from the affected area did not float in water.

Microscopical section showed an approximation of the alveolar surface to a marked degree, with a few red and white blood cells in the alveolar spaces. The interalveolar tissue was normal.

The autopsy findings were otherwise entirely negative.

Attention is called to the relative frequency of this condition and the importance of its recognition from a diagnostic standpoint.

## BACTERIAL ENDOCARDITIS AS A SEQUEL TO SYPHILITIC VALVE DEFECT.

BY LE ROY H. BRIGGS, M.D.

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL, SAN FRANCISCO.

(From the Department of Medicine, University of California Medical School.)

EVER since the advent of subacute bacterial endocarditis as a clinical entity it has been recognized that a previous valve defect was almost a *sine qua non* in the causation of the disease. The vast majority of these defects are of rheumatic origin, with a scattering few due to other infections, congenital heart disease or arteriosclerosis. As a cause of valve defects in general, rheumatic fever comes first, with syphilis probably second; yet with the very frequent occurrence of syphilitic endocarditis of the aortic valve, the combination of subacute bacterial endocarditis and syphilitic endocarditis seems to be a decided rarity. This assertion is made not only on the grounds of personal experience, but also on the basis of a scrutiny of the papers dealing with the subject over the last decade. The valve affected by syphilis is practically always the aortic. Likewise is it very true that in a considerable number of cases of bacterial endocarditis it is this valve alone that has been involved, this point being emphasized by Cotton<sup>1</sup> last year in a report made to the British Medical Research Council. Be this as it may, however, an analysis of the various reports shows an overwhelming predominance of rheumatic lesions and an insignificant incidence of syphilis. Libman seems to be the only author who discusses the relationship at all.

Two of Osler's<sup>2</sup> patients had old aortic lesions alone, one with a history of previous arthritis and one without, but neither had anything suggestive of syphilis and neither came to postmortem. In Horder's<sup>3</sup> elaborate series of 150 cases only 2 gave a history of previous syphilis, although out of 118 examined at necropsy 22 had aortic involvement alone. Nothing is said of the condition of the aorta in these cases, since most were studied in the pre-Wassermann era, before the relationship between syphilis, aortitis and aortic insufficiency was realized. In Billings<sup>4</sup> 14 cases there was only one aortic lesion, and this was definitely rheumatic.

Libman, who has made a more intensive clinical study of bacterial endocarditis than anyone else, several times speaks definitely on

<sup>1</sup> Subacute Infectious Endocarditis, British Med. Jour., 1920, 2, 851.

<sup>2</sup> Chronic Infectious Endocarditis, Quart. Jour. Med., 1908-9, 2, 219.

<sup>3</sup> Infective Endocarditis, Quart. Jour. Med., 1908-9, 2, 289.

<sup>4</sup> Chronic Infectious Endocarditis, Arch. Int. Med., 1909, 4, 409.

this question. In the course of a discussion<sup>6</sup> of valvular disease he says, "The number of instances of valvular defects of rheumatic origin which have become the seat of non-rheumatic or non-syphilitic endocarditis is remarkably large compared to the number of instances in which this occurs on the basis of valvular defect due to lues, considering that lues is such a close second to rheumatism in the causation of valvular disease," and in 1918, in a study of 182 personally observed cases of subacute bacterial endocarditis,<sup>6</sup> he practically repeats this statement. No figures are given, however, of the actual number of instances in which syphilitic valves have subsequently become bacteria-infected. At the symposium on infectious endocarditis at the 1920 meeting of the British Medical Association he again says,<sup>7</sup> "It is interesting to note that the subacute bacterial infections occur mainly on the basis of valvular defects due to the rheumatic virus, and much less in other types, notwithstanding the great frequency of syphilitic valvular defects." Horder<sup>8</sup> at the same meeting states that "any old-standing lesion is good enough to serve as the secondary focus of infection," but he, as well as nearly all those taking part in the discussion, strongly emphasizes the predisposing influence of rheumatic fever.

Cotton<sup>9</sup> has made some interesting studies not only of infectious endocarditis but also of aortic disease, using soldiers attending a British Army heart clinic. He found that 8 per cent of the patients with valvular disease, comprising a series of 55 cases with an average age of thirty years, had subacute bacterial endocarditis, and of these, 33 had aortic lesions alone and 14 had aortic regurgitation as well as mitral stenosis. He makes no mention of preceding syphilitic aortic lesions, however, although 7 of the 55 had a positive Wassermann reaction and 1 a history of syphilis. In his study<sup>10</sup> of 50 cases of aortic insufficiency with an average age of thirty-one years, he obtained a history of rheumatic fever in 27 per cent and syphilis in only 2 per cent. A Wassermann test was done in 35 of these and was positive in 8, but of these all except 1 was over forty years old. He agrees with the commonly held opinion that rheumatic fever is the most important factor in the production of aortic lesions in patients under forty years, while syphilis plays an equally important part after forty years. Although he gives no other data, and in fact does not discuss the matter, one feels that the incidence of preceding syphilitic valvulitis in his 35 cases of bacterial aortic endocarditis was slight, specially since his material was comprised mainly of young men.

<sup>6</sup> Libman, E.: Affections of the Valves of the Heart, *Med. Clin. of North America*, 1917-18, 1, 573.

<sup>6</sup> Libman, E.: Streptococci and Influenzal Endocarditis, *Med. Clin. of North America*, 1918-19, 2, 117.

<sup>7</sup> Libman, E.: *British Med. Jour.*, 1920, 2, 304.

<sup>8</sup> *British Med. Jour.*, 1920, 2, 301.

<sup>9</sup> *Loc. cit.*

<sup>10</sup> Cotton, T. F.: Observations on Aortic Disease in Soldiers, *Lancet*, 1919, 2, 470.

Just why there should be this apparant immunity of the syphilitic valve to secondary infection affords an interesting field for speculation: First, and probably most important of all; the age incidence of the two diseases plays a very considerable part. Syphilitic endocarditis is found most frequently after thirty-five, while bacterial endocarditis occurs under that age in a large majority of the cases. As rheumatic fever is the greatest offender in the production of valve injuries, and is at the same time preëminently a disease of youth and young adult life, it is only natural that it should be the commonest precursor of an infection which selects a damaged valve in a young person as its objective. (2) There is possibly something to be said from the bacteriologic standpoint. The overwhelming majority of the cases of bacterial endocarditis have shown a non-hemolytic streptococcus to be the infective agent. It is by no means improbable that some of these cases owed their early valvular disability to the same organism in an attenuated form, the disease running a milder course with slight valve damage and no septicemic characters, but with streptococci lying dormant in the valve lesions and later lighting up into the terminal infection. This again would cut down the proportionate incidence of syphilis. (3) The anatomic changes occurring in the valves themselves may be a factor. Valve damage means increased vascularity, which has been held to be a predisposing influence in subsequent bacterial infection. This view has been strengthened by Bayne-Jones's<sup>11</sup> demonstration of the valve capillaries, thus affording an anatomic basis for the earlier theories of Köster and Rosenow of the embolic origin of endocarditis. The more vascular is a valve the more readily is it open to later bacterial invasion, and the essential differences between the mode of formation of a verrucose endocarditis and a syphilitic endocarditis speak for a greater vascularization of the former after partial healing has occurred.

The following case is an example of a subacute streptococcus endocarditis which occurred in a patient suffering from syphilitic aortitis and aortic endocarditis, terminating in death and going to necropsy. Only the essential points in the history, examinations and pathologist's report have been set down.

On July 7, 1920, a steamfitter, aged thirty-five years, came to the outpatient department of the University of California Hospital with the complaint of "stomach trouble." His family history was of no bearing. There had been a chancre at fifteen years but no secondary manifestations. He had had five Neisser infections, the last four years before. The left leg had been broken as a boy. He had had a varicose vein operation on the right leg in 1907 and again in 1917. In 1918, the army had rejected him on

<sup>11</sup> Bayne-Jones, S.: The Bloodvessels of the Heart Valves, *Am. Jour. Anat.*, 1917, 21, 449.

account of a "leaking heart valve," the first knowledge he had of any heart difficulty.

In 1917, he began to have pain in the precordial region, radiating down the left upper arm, coming on specially with exertion. This would be followed by some faintness and indefinite feelings of discomfort in the epigastrium. The digestive difficulties continued and brought him to the clinic. After a heavy meal he would be troubled with a sense of oppression in the chest, pain in the upper abdomen, precordium and down the inner side of the left arm to the elbow. The attacks would come on suddenly and last two or three minutes. In the latter part of 1918 he was forced to stop work on account of the pain, although he had had no dyspnea or edema.

On examination it was found that he had lost about forty pounds, although he still looked fairly robust. The pupils were normal. The heart and peripheral vessels showed the characteristic signs of well-marked aortic insufficiency: enlargement to the left, widened arch, at the base a to-and-fro murmur, with the diastolic element very loud and a loud systolic murmur at the apex. All peripheral arteries pulsated vigorously; there was a typical Corrigan pulse, capillary pulsation, pistol-shot sound over the femorals and a blood-pressure of 120/40. The rate was 62 and regular. The abdomen showed nothing. There was a scar on the penis and the blood Wassermann was triple positive. He was given five small doses of salvarsan and some mercury salicylate injections, eventually drifting away from the clinic during the latter part of September, somewhat improved.

Nothing more was heard of him until August 1, 1921, when he entered the University of California service of the San Francisco Hospital. After leaving the clinic conditions apparently had been stationary until May, when he began to lose weight and noticed on the pads of his fingers occasional red painful spots which would last a day or so and then disappear. Since the middle of June he had been growing weaker, with night-sweats and dyspnea. There had been a loss of sixty pounds, and although he had gone to various hot springs in the hope of relief, he had failed progressively.

On examination he was quite sick-looking and presented a great contrast to his appearance of a year before. The heart was about the same but the peripheral pulsations were less marked. A few petechiæ were present over the neck and shoulders and there were rare retinal hemorrhages. There was no clubbing of the fingers. For the next two months he ran a septic type of fever, varying from normal to 102°. Petechiæ were constantly present over the neck and shoulders and a number of painful evanescent erythematous nodules appeared on the pads of the fingers. The spleen was not felt until September 1, when a soft enlargement

was noted, persisting until death. The systolic murmur at the apex disappeared permanently about this time. Anemia was progressive, going from 80 per cent hemoglobin and 5,000,000 reds at entrance to 35 per cent hemoglobin and 2,500,000 reds at the lowest point. There was a slight leukocytosis with a relative increase in the neutrophiles. The blood Wassermann was still triple positive. On account of considerable mental confusion at entrance a lumbar puncture was done, which showed a cell count of 32 normal globulins, negative Wassermann and a luetic colloidal gold curve. Microscopic hematuria was constant over a number of urine examinations. Three blood cultures were taken during August, each resulting in the isolation of a long-chained non-hemolytic streptococcus which did not form pigment on blood agar and which was agglutinated by the patient's serum in dilutions up to 1/800.

His course was steadily downward and he became very thin and weak. Toward the last there was marked cardiac dilatation, small amounts of fluid in both pleural cavities and passive congestion at both lung bases. He died October 5, 1921.

Necropsy was done by Dr. G. Y. Rusk and portions of his report germane to the subject are quoted.

*Anatomic Diagnosis.* Acute verrucose endocarditis, involving all the cusps of the aortic valve, with perforation of the right posterior aortic cusp and with extension of the process to the anterior cusp of the mitral valve, with small aneurysmal herniation of the same. Syphilitic aortitis with dilatation of the first part of the aorta and involvement of the ring of the aortic valve with insufficiency. Marked atheromatous degeneration with calcification of the first part of the aortic arch. Myocardial fibrosis. Subacute degeneration of subendocardium of the left ventricle. Diffuse cardiac hypertrophy. Cardiac dilatation, involving particularly the left ventricle, less markedly the left auricle and the right ventricle. Relative dilatation of the aortic and mitral orifices. Hydroperitoneum, hydropericardium and bilateral hydrothorax. Diffuse subperitoneal edema. Chronic passive congestion of the lungs. Pulmonary edema. Compensatory pulmonary compression atelectasis. Slight diffuse bronchitis. Recent infarcts in the spleen. Old scars in the spleen. Old infarct in each kidney. Acute diffuse nephritis. Secondary anemia. Thromboses in periprostatic plexus. Undescended and atrophied left testis. Emaciation.

*Heart.* Greatly enlarged, 550 gms. Epicardium devoid of fat, edematous in appearance, presents on the anterior surface of the left ventricle toward the apex two small, irregular, slightly depressed, scar-like areas about 3 mm. in diameter. Myocardium pale brown, rather flabby and shows definite patches of fibrosis in the left ventricular wall near the apex. Left ventricular wall measures 1 to 1.25 cm.; right, 3 to 5 mm. in thickness. Endo-

eardium pale; that of the left ventricle presents a fine diffuse mottling resembling fat deposits; section in this region into underlying subendocardial tissues shows these apparently involved in a degenerative process to a depth varying from 1 to 2 mm., and here the tissue in question appears grayish yellow, opaque and softer than normal.

*Valves.* Adherent to all of the cusps of the aortic valve are relatively large, yellowish-brown, verrucose masses, the largest measuring 1.5 cm. x 1 cm. x 0.75 cm. These are attached to the ventricular surfaces of the cusps, favoring particularly their line of closure, and are composed of a friable, soft, granular material. In the right posterior cusp, involving the end next to the left posterior cusp, is a large opening which apparently represents an ulcerative perforation. The cusps themselves are not unusually thickened or deformed. There is, however, a distinct spacing at their angles so that the cusps are separated from each other by an average distance of 2 or 3 mm. From the anterior cusp the vegetations proceed as a direct, though somewhat interrupted, line down on to the ventricular surface of the anterior cusp of the mitral valve. The corresponding area on the auricular surface of this cusp presents a round elevation, 0.75 cm. in diameter, which on further examination is seen to be a small aneurysmal herniation, the result of a weakening of the wall of the cusp due to the vegetations. Attached to the free border of the same cusp is noted a group of chordæ tendineæ which apparently have ruptured and whose ends are covered with vegetations. The cusps of the mitral valve otherwise appear negative. Measurements: Tricuspid, 12 cm.; pulmonary, 7 cm.; mitral, 12 cm.; aortic, 8 cm.

*Heart Cavities.* The left ventricle is greatly dilated, resulting in a marked blunting of the heart apex and a flattening of the papillary muscles. The left ventricular cavity extends downward 3.5 cm. beyond the apex of the right ventricle. The latter cavity likewise presents some dilatation, particularly in the region of the conus. The left auricle is somewhat dilated.

*Coronary Arteries.* The beginning of the right coronary is narrow, but except for this both coronary vessels appear normal. In proportion, however, to the size of the heart the caliber of the descending branch of the left coronary is relatively small.

*Aorta.* The arch is dilated and measures 8 cm. in circumference. The first portion of the arch shows a marked striation of the intima as well as numerous atheromatous patches, many associated with large, thin, calcareous plaques. These changes appear limited to the first 4 cm. of the aorta, which is definitely increased in thickness, averaging 4 mm. as compared with 1 mm., the thickness of the rest of the aortic arch. The remainder of the aorta, including the thoracic and abdominal portions, is in excellent condition, showing only a few scattered patches of atheroma.

*Summary.* From a study of the literature it would seem that the sequence of bacterial endocarditis on a syphilitic endocarditis is a decided rarity, despite the frequency of the latter condition and the fact that the former infection often has a selective action on the aortic valve. No reason can be assigned for this, although the age incidence of the two diseases probably plays some part. Another factor may be the increased vascularity of the valve previously damaged by rheumatic fever as compared with that damaged by syphilis. A case is reported of an individual suffering from a typical syphilitic aortitis and aortic endocarditis. One year later the patient enters the hospital with a non-hemolytic streptococcic endocarditis, which pursues the usual course and terminates in death. At necropsy a characteristic syphilitic aortitis with involvement of the aortic ring is found, together with an acute verrucose endocarditis of all the aortic cusps and perforation of one, with an extension into one mitral leaflet.



## REVIEWS.

---

A MANUAL OF CLINICAL LABORATORY METHODS. By CLYDE LOTTRIDGE CUMMER, PhB., M.D., Associate Professor of Clinical Pathology, School of Medicine, Western Reserve University; Associate Clinical Pathologist, Lakeside Hospital; Director of Medicine and Visiting Physician, St. John's Hospital; Director of Laboratories, St. Alexis Hospital, Cleveland, Ohio. Pp. 484; 136 engravings and 8 plates. Philadelphia: Lea & Febiger, 1922.

THE author opens his treatise with a very detailed chapter on the study of the blood. This chapter includes microscopic, serologic and chemical examination methods given in full. All the modern chemical methods for blood are introduced in very clear and definite form; the concise and systematic grouping of the steps in making a chemical examination of the blood render the book of great value to the student. Examination of the urine is briefly surveyed; an excellent chapter on tests for renal function is included. Gastric contents, feces, sputum and spinal fluid examinations are each given a brief chapter and bacteriological methods as a whole are touched upon. There is a very useful appendix which covers formulas for the most commonly used stains, a list of apparatus to be assembled for routine clinical laboratory work, a useful table for equivalents of the metric and common system and one for conversion of Centigrade to Fahrenheit degrees. The book is written clearly and concisely and will be of much value to the laboratory worker, even if for the chapters on blood alone. An extensive bibliography is given, bringing the subject-matter up to date and the book is well indexed.

E. Q.

---

PAPERS FROM THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH AND THE GRADUATE SCHOOL OF MEDICINE OF THE UNIVERSITY OF MINNESOTA, COVERING THE PERIOD OF 1915-1920. Pp. 695; 203 illustrations. Philadelphia and London: W. B. Saunders Company, 1921.

THIS book is a collection of papers by students and teachers in the Mayo Foundation and Medical School, and is not to be con-

fused with the *Collected Papers of the Mayo Clinic*. Nearly all of the papers were originally in the form of theses presented by graduate medical students in partial fulfilment of the requirements for the degree of Master of Science or Doctor of Philosophy and are the result of research work. Abstracts by the authors take the place of many of the original articles, some of which have been previously published in the current literature. The list of contributors contains sixty-four names, and the diversity of subjects treated may be gathered from a glance at the titles of some of the eleven papers grouped under the heading of Alimentary Tract. These include: "The Morphology of the Digestive and Respiratory Tracts in a 20 mm. Pig Embryo;" "Some Clinical and Experimental Observations on Gastric Acidity;" "Use of the Gas-chain Method;" "A Study of the Arteries Supplying the Stomach and Duodenum and their Relation to Ulcer;" "Multiple Polyposis of the Intestinal Tract;" "Clinical Studies in Abdominal Disorders." In publishing a work of this kind the medical school advances both its own and its students' interests, while giving to the profession the results of studies which would otherwise be known only to a few. It is surprising, therefore, that more publications of this nature have not appeared from our medical schools. J. H. A.

---

THE SURGICAL AND MECHANICAL TREATMENT OF PERIPHERAL NERVES. By BYRON STOOKEY, Associate in Neurology, Columbia University; Assistant Surgeon, New York Neurological Institute; Assistant Professor of Neuro-Surgery, New York Post-graduate Medical School and Hospital. With a Chapter on Nerve Degeneration and Regeneration, By G. CARL HUBER, M.D., Professor of Anatomy, University of Michigan. Pp. 475; 217 illustrations, (8 in color and 20 charts). Philadelphia and London: W. B. Saunders Company, 1922.

The recent war may have served to overemphasize the frequency of peripheral nerve lesions, but their importance is manifest. There is no field of surgery in which there has been such a lamentable lack of intelligent understanding of the very nature of these lesions on the part of all but a very few specially trained in this field. In the title of this book the author gives evidence of an appreciation of the fundamental necessities of handling lesions of the peripheral nerves. Corrective surgery must be done, but it will fail unless combined with the proper mechanical treatment. The author is entirely right: Peripheral nerves should be looked upon as extensions of the central nervous system and should be handled by surgeons trained in the anatomy, physiology, pathology and surgery of the central nervous system. Nerve tissue is the most

highly specialized tissue in the body and is the least tolerant of trauma. It cannot be handled therefore in the same way that one would handle tendons.

Each subject, such as the anatomy, methods of nerve repair, direct nerve implantation and direct muscular implantation, tubulization, etc. are carefully and thoroughly considered. The chapter on Nerve Degeneration and Regeneration by Dr. G. Carl Huber is a distinct addition to the book. No one more than Dr. Huber has an authoritative right to speak on this subject. If one is inclined to be hypercritical, it might be said that some will feel the principal object in describing an operative procedure is to give a dispassionate description of its technic rather than either to omit its description because the author does not approve of it or to overemphasize some other technic which does meet with the author's approval. The reviewer finds himself, however, so in accord with the author in stating his preference for certain operative procedures that this objective is not a serious one. The illustrations are excellent and altogether the reviewer can heartily commend this book to one interested in peripheral nerves. The reviewer has found much to praise and almost nothing to criticize in this book.

J. S. R.

---

INTRODUCTION TO DERMATOLOGY. By NORMAN WALKER, LL.D., M.D., F.R.C.P., Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Seventh edition. Pp. 366; 80 illustrations. New York: William Wood & Company, 1922.

This is one of the standard text-books on diseases of the skin, somewhat smaller in size than the average dermatological text-book. The fact that seven editions have appeared indicates very clearly that the book may be recognized as one of the acceptable text-books on the subject. The new edition contains several new plates as well as a considerable amount of new material.

J. H. M., Jr.

---

NEOPLASTIC DISEASES. A TREATISE ON TUMORS. By JAMES EWING, M.D., Sc.D., Professor of Pathology at Cornell University Medical College, New York City. Second edition. Pp. 1054; 514 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

To those especially concerned with the study of tumors, this book has now become well-nigh indispensable. Amid the fog of medical text-books, so many of which appear to be written primarily in response to the energetic publisher's demand, and only secondarily

because the author had something valuable to contribute, Ewing's *Neoplastic Diseases* stands out like a beacon. A review of the first edition, written from the practitioner's standpoint, was printed in this journal in 1919. Let it suffice to say that the pathologist's commendation must be even greater. The second edition has added thirty-three more of the excellent photomicrographs and considerable new data to the chapters on fibroma, sarcoma of bone and bone marrow and endothelioma.

E. B. K.

---

AIDS TO MEDICINE. By BERNARD HUDSON, M.D. (CAMB.), M.R.C.P. (Lond.), Swiss Federal Diploma, Physician-in-charge of the English Sanatorium at Montana, Switzerland. Third edition. Pp. 370; 11 illustrations. New York: William Wood & Company, 1921.

THIS small handbook is prepared for the purpose of supplying the student with a book on medicine of a size convenient to carry around in order to refresh his memory from time to time. It apparently fulfils these requirements.

J. H. M., JR.

---

MODERN METHODS OF TREATING FRACTURES. By E. W. H. GROVES, Surgeon to Bristol General Hospital, Consulting Surgeon to the Lessham Hospital. Second edition. Pp. 435; 296 illustrations. New York: William Wood & Company, 1922.

FIVE years after the first edition appears this, the second edition, in which the book has largely been rewritten. The majority of the illustrations are new and the entire subject of the treatment of fractures has been brought up to date in every sense of the word. The entire subject of bone grafting is considered afresh—presenting the subject experimentally and clinically. An attempt has been made to present all good modern methods, so that the book is one for ready reference.

The author's views are sane, sound and mechanically correct. His one statement, that fractured bones must be treated by neutralizing the muscle pull in all cases, shows that he knows the principles thoroughly. When he further adds: "Until fractures receive the same special consideration accorded other surgical conditions and cease to be regarded as mere encumbrances of general surgical wards, no great progress can be made"—he shows that he has the actual and practical welfare of the broken bone at heart. He shows that the treatment of a fracture is merely begun at the time of the so-called reduction.

E. L. E.

DISEASES OF THE EYE. By GEORGE E. DE SCHWEINITZ, M.D., LL.D., Professor of Ophthalmology in the University of Pennsylvania; Ophthalmic Surgeon to the University Hospital; Consulting Ophthalmic Surgeon to the Philadelphia General Hospital and the Orthopedic Hospital and Infirmary for Nervous Diseases; Colonel, M.R.C., U. S. Army. Ninth edition. Pp. 832; 415 illustrations. Philadelphia: W. B. Saunders Company, 1921.

THE ninth edition of Dr. de Schweinitz's book on ophthalmology has been entirely revised, reset and reprinted. It is, therefore, virtually a new book with the added advantage that the author has had the benefit of the experience acquired in the preparation of the other volumes. A critical review of this work hardly seems necessary. It has been universally recognized in every English-speaking country as a standard text-book on the subject and has been accepted for many years as an ideal book on diseases of the eye.

J. H. M., JR.

---

SURGICAL CLINICS OF NORTH AMERICA. PHILADELPHIA NUMBER. Vol. II. Pp. 331; 145 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THIS, the Philadelphia number, is contributed to by some of the best-known surgeons in the city, if not in the country. Most of the material is presented in a clear, concise and interesting manner. The greater portion of the work deals with important daily questions and it is interesting and instructive to be able to follow the reasoning of the man at the helm.

Just one or two of the articles make the book worth much to the reader, though this value were not enhanced by a dozen others.

The one criticism, if it could be so-called, is that space is given to much of unimportance in the minor details, which however from a teaching standpoint may be rightly considered commendable.

E. L. E.

---

THE PATHOLOGICAL GALL-BLADDER ROENTGENOGRAPHICALLY CONSIDERED. By ARIAL W. GEORGE, M.D., AND RALPH D. LEONARD, M.D. One hundred and thirty-five roentgen-ray studies on forty-five full-page plates, of which three are actual photographs, and two text illustrations.

THE first part of this work, Volume II of the *Annals of Roentgenology*, is a monograph on the radiographic study of the pathological gall-bladder. In it are discussed technic, interpretation, with all the factors entering into it, and the operative findings in

128 cases. The second part, or Atlas section, is a handsomely illustrated record of one hundred and thirty-five roentgen-ray studies showing the usual and unusual conditions encountered in the examination of the gall-bladder region. The captions of the illustrations and the introductory text of each division are printed in English, French, and Spanish. The space allotted the reviewer precludes an exhaustive criticism of this splendid volume. Suffice it to say that the authors, recognized authorities, have produced what cannot help but be a very valuable reference book.

J. D. Z.

---

THE PREVENTION OF MALARIA IN THE FEDERATED MALAY STATES: A RECORD OF TWENTY YEARS' PROGRESS. By MALCOLM WATSON, M.D., C.M., D.P.H., Chief Medical Officer, Estate Hospital's Association, Klang, F.M.S.; late Senior District Surgeon, F.M.S. Medical Service; with contributions by P. S. HUNTER, M.A., M.B., D.P.H.; Deputy Health Officer, Singapore, and A. R. WELLINGTON, M.R.C.S., L.R.C.P., D.P.H., D.T.M. & H., Senior Health Officer, Federated Malay States, and a preface by SIR RONALD ROSS, K.C.B., K.C.M.G., F.R.C.S., D.P.H., M.D., LL.D., D.Sc., F.R.S., NOBEL LAUREATE. Second edition. Pp. 381; 115 illustrations. New York: E. P. Dutton & Company, 1921.

FEW who have not actually lived in the tropics realize the magnitude, the importance, or the complexity of the problem of malaria prevention in these lands. Twenty years of study and successful effort have qualified the author to speak with authority upon the subject of mosquito control in the Malay States. He pictures the problems which faced him as a member of the Malaria Advisory Board appointed by the British government, and as health supervisor of rubber estates scattered over an area twenty times as great as the Panama Canal Zone. He describes in minute detail the attempts which were made to solve these problems, his failures and his successes, and records the observations which he made at the time.

This work will stand as one of the milestones in the history of malaria control and the book is therefore of interest from the historical standpoint. To those confronted with the problem of mosquito control in the tropics it will be an invaluable aid, and wherever the drainage problem has to be met in our war upon the mosquito it will be of value as a reference book. The last five pages give the author's conclusions and are well worth reading by anyone interested in the prevention or treatment of malaria.

J. H. A.

**OPIATE ADDICTION: ITS HANDLING AND TREATMENT.** By EDWARD HUNTINGTON WILLIAMS, M.D., formerly Associate Professor of Pathology, State University of Iowa; Assistant Physician, New York State Hospital System; Special Lecturer on Criminology and Mental Hygiene, State University of California. Pp. 194. New York: The Macmillan Company, 1922.

HARDLY a page of this brief treatise is without its human interest and practical value. The various methods of rapid withdrawal, including those popularized by Lambert, Bishop, and others, are outlined with admirable clarity. The author discusses the gradual withdrawal of opium even more fully and in a manner which will appeal to the practitioner who needs help in the management of his addiction cases. The pages reflect the author's intimate knowledge of the language and habits of the underworld, and of the operation of the Harrison Law. In this connection it is regrettable that the reader is not informed regarding the *modus operandi* by which dope peddlers secure the drug, since here must be the point of attack if the illicit traffic is to be stamped out.

J. H. A.

**RADIUM THERAPY.** By FRANK EDWARD SIMPSON, A.B., M.D., Professor of Dermatology, Chicago Polyclinic; Adjunct Clinical Professor of Dermatology, Northwestern University Medical School; Director of the Frank Edward Simpson Radium Institute. Pp. 391; 166 illustrations and 30 tables. St. Louis: C. V. Mosby Company, 1922.

THE limitation of space precludes full consideration of this important volume. The author has presented the results of his vast experience with the physical, experimental, biological and therapeutic aspects of radium in a concise and comprehensive style. In addition, the volume gives evidence that the author has thoroughly studied the literature bearing upon radium, its application and effects, as he has quoted frequently from an extensive bibliography. The book is a valuable contribution to the literature of radiology and should be owned and studied by every internist and general surgeon.

In Chapter XIII, in which the author considers the important subject of dosage, valuable tables are given together with thorough explanations. Chapter XV, dealing with the application of radium in general surgery, is admirably presented, but it might be mentioned that there is some difference of opinion among eminent authorities as to the best time to operate following preoperative radiation.

On the whole the book is logically arranged, with clear readable type, and contains an abundance of excellent illustrations.

E. P. P.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**A Graphic Method for Calculating Woodyatt Diabetic Diets.**—HANNON and McCANN (*Bull. Johns Hopkins Hospital*, 1922, 33, 119), after a brief discussion of Woodyatt's practical application of Shaffer's work on antiketogenesis, present a graphic chart which has been found of great service during the past year at the Johns Hopkins Hospital in facilitating the preparation of diabetic diet prescriptions. Starting with the patients' estimated calorie requirement, with the aid of their chart a maintenance diet may be rapidly worked out which will supply the desired percentage of protein and at the same time preserve a safe balance between the ketogenic and antiketogenic substances found in the diet. They also point out the fact that a diet containing less protein permits the use of much greater amounts of free carbohydrates.

---

**The Toxicity of Botulinus Toxin by Mouth.**—BRONFENBRENNER and SCHLESINGER (*Jour. Am. Med. Assn.*, 1922, 78, 1519) state that botulism, a comparatively rare disease in this country, is apparently increasing in prevalence. The disease is caused by eating food contaminated with botulinus toxin. This toxin, elaborated by *Bacillus botulinus*, is quite analogous to the toxins of tetanus and diphtheria. They resemble one another in many respects, but differ quite markedly in others. The toxin of *Bacillus botulinus* is analogous to other toxins in all the essential properties, identifying it as a true bacterial toxin. It can be isolated from cultures by filtration. It kills experimental animals in small doses with symptoms characteristic of the disease. It is thermolabile and it is neutralized by a specific



type antitoxin. In the case of *Bacillus botulinus* one is dealing with a group of bacteria, the members of which are capable of producing the same symptoms, and which have similar cultural characteristics, but which are different in their immunological reactions. Experimentally botulinus toxin is many times more potent than either of the analogous toxins. The symptoms of botulism appear after a period of incubation, but this period is a matter of minutes as compared to hours in the case of tetanus and diphtheria. Neither tetanus nor diphtheria toxin is poisonous when taken by mouth, whereas botulinus toxin is toxic when taken by mouth in very small doses. The toxins of the first two bacteria are destroyed by the digestive processes which go on in the stomach and duodenum. The botulinus toxin, however, resists the acidity of the stomach for many hours, and, furthermore, trypsin and pepsin have no destructive effect upon it. In view of the experiments carried on by the authors one must conclude that the placing of crude filtrate in the stomach consists essentially in an acidification *in vivo* with a resulting increase in potency similar to that which can be accomplished by acidification in a test-tube. The failure of the digestive processes to alter the toxin enables direct absorption to occur through the digestive tract. Besides differing from other bacterial toxins in that it is toxic by mouth, botulinus toxin differs from them in its reaction with ethyl alcohol. Precipitation of tetanus and diphtheria toxin with alcohol produces a very refined substance, while the botulinus toxin by precipitating it with alcohol is destroyed. In several recent outbreaks of food poisoning some of those exposed escaped altogether or had very mild symptoms. The investigators of the outbreaks discovered that those who had escaped symptoms had partaken rather freely of alcoholic beverages during the meal.

---

**Pituitary Extract Intranasally in Diabetes Insipidus.**—BLUMGART (*Arch. Int. Med.* 1922, 29, 509) describes a method of administering pituitary extract by intranasal spray, thus avoiding the necessity for frequent hypodermic injections in cases requiring continued treatment. Extract of the posterior lobe of the pituitary sprayed intranasally in a case of diabetes insipidus was found to check the polyuria and polydipsia as effectually as did hypodermic injection. Administration by mouth or rectum proved quite ineffectual. Given by mouth in tablets coated with phenylsalicylate the extract was likewise without effect. Histamin failed to modify thirst or polyuria, no matter how given. The exact mechanism of absorption is undetermined. It is pointed out, however, that there is an almost direct communication between the lymphatics of the nasal mucosa and the subarachnoid space.

---

**Hypophysectomy in Dogs and Cats.**—CAMUS and ROUSSY (*Compt. rend. Soc. de biol.*, 1922, 86, 1008) describe the technic of the buccal route and of the temporal route used by them in approaching the hypophysis. The operative mortality was high from meningitis, hemorrhage or brain injuries. Some of the animals died within several days, others within several weeks and still others lived for several months. Sixteen animals were sacrificed after a long time and ten or more were still living and apparently well. Total removal of the hypophysis was attempted at

each operation and this was controlled by thorough examination of the material removed at operation and by careful macroscopic and microscopic study of the base of the brain in the animals that died or were sacrificed for study. From their researches they conclude that for adult dogs and cats the hypophysis is not necessary for the maintenance of life.

---

**Emetic Action of Digitalis.**—HATCHER and WEISS (*Arch. Int. Med.*, 1922, 29, 690) showed in their convincing experiments that emesis resulted after the intravenous administration of a digitalis body when the carotid and vertebral arteries were tied, although very little of the poison could have reached the vomiting center. On the other hand perfusion of brain and medulla with defibrinated blood to which euabain had been added did not produce nausea or vomiting, nor was direct application of digitalis bodies to the vomiting center followed by emesis. The application of 0.0001 mg. apomorphin hydrochlorid to the vomiting center, however, was promptly followed by vomiting. Further experiments showed that when the nerve supply of the heart is intact emesis can be produced by the intramuscular injection of a digitalis body, but that these bodies are not capable of inducing vomiting when all of the nervous connections between the heart and the medulla are cut. These results are interpreted as evidence that the digitalis bodies produce emesis by a reflex, protective in nature, from the direct action of the drug on the heart itself. Impulses appear to pass from the heart to the medulla chiefly by way of the sympathetic but to some extent by way of the vagus. Such a conception of the mechanism of the emetic action of digitalis bodies obviously means that the effect of the drug on the heart cannot be dissociated from its emetic effect.

---

**Divided Meals for Severe Diabetics.**—GRAY. **Multiple Meals in Severe Diabetes.**—MURAYAMA (*Boston Med. and Surg. Jour.*, 1922, 186, 23). These authors present cases which show that in some instances at least the use of six or more meals a day instead of three is followed by an increase in the sugar tolerance for severe cases of diabetes. Absolute proof of cause and effect is neither given nor contended, but it is very strongly suggested that the severe diabetic's ability to metabolize food may be stimulated by small meals, frequently given. Gray speculates as to the cause of these apparently gratifying results. His theory of divided meals appears to be activation of the liver or pancreas by a small preliminary meal of carbohydrate given one or two hours before each main meal; the organism, being then in action at the time of that regular meal, responds to the food load more vigorously than with the every-day three-meal schedule. Relevant statements found in a search of the literature are briefly reviewed. The method which is outlined as follows is advocated as having practical value: (1) Intervals between meals, two and one-half hours, never less, except that the first activating meal (the keystone of this technique) may be taken any time between one and two and one-half hours before the regular breakfast; (2) caloric value of meals—of the extras the first must be the smallest meal of the day. Of the main meals the regular breakfast is to be the smallest; (3) composition of the activating meals: practically pure carbohydrate, generally most conveniently administered, as an orange, a grapefruit or 5 per cent vegetables.

## SURGERY

---

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

---

**Von Recklinghausen's Disease or Osteitis Fibrosa.**—YOUNG and COOPERMAN, (*Ann. Surg.*, 1922, 75, 171) say that osteitis fibrosa is a distinct pathological entity characterized by a fibrous metaplasia of bone. Under this term may be included benign bone cysts, giant cell sarcoma of the epulis type, hemorrhagic osteomyelitis and the generalized form (von Recklinghausen's disease). Two types of the disease are recognized—a local and a general type. Local osteitis fibrosa and benign bone cysts are dependent upon trauma in a great majority of instances. The general form is dependent upon grave nutritional disturbances. Cysts, osteitis fibrosa cystica and giant cells may occur in the same bone. The giant cell content is not prognostic of malignancy. Diagnosis of osteitis fibrosa is based upon the long duration of this process with very vague symptomatology, the frequency of spontaneous fractures and upon roentgen-ray examination. Very often microscopical examination of pathological sections is necessary to clear up the diagnosis. The local form of the disease is benefited by curettage and bone transplant. The type showing multiple lesions must be given constitutional treatment directed toward the underlying constitutional disturbance. If the lesions be accessible curettage and bone transplant may be employed.

---

**The Results of High Ligation of the Cystic Duct in Cholecystectomy.**—HARTMAN, SMYTH and WOOD (*Ann. Surg.*, 1922, 75, 203) say that the cystic duct stump usually dilates to form a pseudo-gall-bladder. We may therefore get a recurrence of the symptoms after a cholecystectomy. Where the cystic duct is ligated flush with the common duct, there is a general dilatation of all ducts, indicating that there is pressure in the biliary system. While the gall-bladder is not essential to life, it seems to have a very definite function of storing bile and acting as a tension bulb to regulate pressure in the biliary system. Nature endeavors to restore the normal condition in the biliary system after the removal of the gall-bladder by dilating and enlarging the ducts including the cystic duct stump.

---

**A Comparative Analysis of 213 Forearm and Leg Fractures.**—BIZARRO (*Ann. Surg.*, 1922, 75, 221) says that backfire is one of the commonest causes of forearm fracture and slipping or twisting the ankle the commonest mechanism of leg fracture in these series. Fracture of the radius alone is the commonest in the forearm and fractures of both tibia and fibula commonest in the leg. The radius was fractured in 84

per cent of cases of forearm (single and double) fractures and the fibula was fractured in 79 per cent of cases of leg (single and double) fractures. The lower third of the radius is the most fragile part of the bone and was fractured in 91 per cent of single radial fractures and the lower third of the fibula is the weakest point of the bone and was fractured in 88 per cent of single fibular fractures. The upper end of the ulna is the commonest seat of single ulnar fractures and the lower third of the tibia the commonest place of single tibial fractures. The lower third of the radius and ulna is the commonest seat of double forearm fractures and the lower tibial third, the commonest level of the leg double fractures. The classic fractures of Colles, Pott, Dupuytren, as conceived by these authorities are comparatively rare. Epiphyseal fractures are commoner at the wrist. The marginal fractures of the radius (Barton, Letenneur) are rarer than the marginal tibial fractures. Longitudinal or medullary splits are commonest in the fibula. Chauffeur's fracture may occur at the upper end as well as at the lower end of both radius and ulna. The commonest direction of the fibular fractures is from before backward and upward and is usually incomplete. Fractures of the tubercle appear to occur in a growing bone and fractures of the tibial tuberosity in an adult bone. Fractures of the upper half of the ulna, radius, tibia and fibula diaphysis are usually due to direct trauma.

---

**Duodenectomy (An Experimental Study).**—MANN and KAWAMURA (*Ann. Surg.*, 1922, 75, 208) say that their experiments show that the duodenum is not necessary for life and the fact that noteworthy changes were not observed makes it appear that its function does not differ greatly from that of the rest of the intestinal tract. Only one positive finding was obtained. In two of the dogs a large ulcer was found on the jejunal side of the suture line of the gastrojejunal anastomosis. In one of the animals the ulcer perforated, causing peritonitis and death. Since peptic ulcer of the subacute or chronic type is very rare in the dog, it seems significant.

---

**The Treatment of Fractures.**—SMITH (*Brit. Med. Jour.*, April 2, 1921, p. 483) says that conservative treatment by splinting has again come into its own purely on account of the excellent results gained by standardized methods in thousands of gunshot compound fractures obviously unsuitable for operative fixation of the fragments. Where experience tells one that good functional results cannot be obtained by splinting alone, we should be prepared to operate, provided we have experience in that method also. The main essential is that, following general principles guiding treatment, we shall pay the strictest attention to details in whatever method we adopt. The author advocates the principles laid down by H. O. Thomas and Sir R. Jones in the mechanical treatment of fractures, namely, a fracture is a potential deformity and must be regarded as such. Strong, steady, fixed extension with corresponding counterextension is required, as distinguished from forcible, intermittent pull succeeded by a period of muscular relaxation; correct alignment in conjunction with obliteration of shortening; avoidance of rigid, circular compression, which tends to produce ischemia. Union may be delayed—this is sometimes unavoidable; but there is a vast difference between delayed union and non-union.

Union of a fracture does not imply its consolidation. Both mal-union and non-union are common occurrences and are often related. In fractures of the neck of the femur the angle between neck and shaft is reduced and a condition of coxa vara results. In fracture of the upper third of the shaft the upper fragment is abducted, the lower fragment pulled up to the inner side of the upper one, and a shortened, bowed femur results. In fractures of the middle of the shaft there is a concavity forward instead of the normal convexity. The same deformity is present in the lower fourth of the shaft. Fractures in upper third of the leg may lead to a high bow-leg. Fractures of the middle third may result in knock-knee with either inversion or eversion of the foot. Fractures of the lower end of the lower third of both bones generally end with a valgoid deformity of the foot with an internal rotation. These are the commonest reasons for mal-union: being too sparing with traction; inefficient splinting, and the effect of allowing body weight to fall on recovering bone too soon. If there be pain over the site of a fracture of old standing, especially on digital pressure, unsound union may be suspected, and if this pain be accompanied by an exuberant callus formation the diagnosis is absolute. Some fractures are slower than others in beginning to unite. Too much interference in the way of constantly moving the fragments to see whether union is occurring is apt to end in non-union. In comminuted fractures the wholesale removal of bone fragments is apt to result in non-union also. Treatment by what Thomas called damming and hammering is of assistance. In fractures of the lower extremity, operation should be postponed until the effect of the patient getting about with the aid of an appliance has been tried, for the number of stubborn non-unions that respond to this simple procedure is surprising. The need for operation having arisen, the question whether this should consist of freshening the fractured ends and bone-plating or bone-grafting is one which depends upon personal choice. Likewise, the question what fractures should be treated at once by operation, and which by splinting, must be answered by the individual surgeon. The author generally operated on spiral fractures of the lower third of the leg by means of inlay grafts, but plating is equally satisfactory in skilled hands. Fractures of the patella in transverse axis are treated by wiring, as are also fractures of the olecranon where there is a large gap with rotation of the fragments. Scaphoid fractures are also operated where the proximal fragment prevents full hyperextension of the wrist and where there is palmar dislocation of the semilunar bone; removal of the proximal portion of the scaphoid is generally sufficient. All other fractures are treated by means of splinting or posture or both combined in some cases with rigid extension and counterextension. Fractures of the neck of the femur and the upper fourth of the shaft are best treated in the double Thomas frame with extension straps on both legs, the affected limb being widely abducted. The groin on the sound side gives adequate counterextension. In old people it is advisable to fit a walking caliper, made one-half inch too long, and allow the patient up on crutches. Careful nursing is essential in cases treated on a frame: the back must be carefully rubbed with talcum twice daily—the flat of the hand being carefully interposed between the skin of the back and the pad of the frame; an alcohol rub twice weekly is also necessary; with these rules strictly

obeyed, no skin trouble need be feared. Fractures of the middle and lower portions of the shaft of the femur, fracture of the condyles and fractures of tibial tuberosities and shaft in the upper three-fourths are all treated in the Thomas knee-bed splint. The use of calipers, ice-tongs and Steinman's pins to produce traction are complications which are only applicable in hospitals, in the hands of experts, and in a large percentage of cases are unnecessary. Fractures of the leg, with the exception of Pott's fracture, are treated on the same lines, and fractures involving the knee-joint require adequate restoration of fragments by manual pressure combined with traction. The reduction of a Pott's fracture is of greater importance than the splinting. Forceful traction with the foot in extreme extension, combined with a downward pull on the leg and an upward pull on the heel to reduce the backward displacement of the foot, should reduce the deformity, but occasionally it is necessary to divide the tendo Achillis. The foot is then forcibly inverted into an overcorrected position. In fractures of the tarsus, when reduction is complete, all that is necessary is for the foot to be kept at a right angle. Fractures of the humerus in the region of the shoulder-joint; if inefficiently treated, show limitation of abduction and external rotation. Fractures in the region of the elbow-joint are apt to result in defects of flexion and supination: supination is often deficient in fractures of both bones of the forearm; the deformity of a mal-united Colles' fracture with limitation of wrist movement, of pronation and supination and of finger flexion is well known. Fractures of the anatomical neck of the humerus are best treated by a wrist sling which allows the weight of the arm to act as an extension, with a pad in the axilla to produce slight abduction of the upper arm. In treating separation of the upper humeral epiphysis, in childhood or adolescence, it is advisable to abduct the arm to a right angle and to rotate it outward until the hand is level with the mouth, and then to immobilize the arm in this position either by one of the humerus abduction splints or in plaster. Impacted fractures of the surgical neck are best reduced by the method of Thomas: The patient is seated upon a chair and a roller-towel is passed under the axilla and fastened to a coat-hook or nail; a wrist sling is fastened around the neck and a clove hitch is made fast to the elbow, with a long loop which comes to within a foot of the floor and which acts as a stirrup for the operator's foot; extension is obtained while both hands of the operator are free for manipulation; the axis of the pull is brought to the abducted position, and when reduction appears complete the arm is forced upward and reimpacted; treatment is same as that for the anatomical neck except that a larger axillary pad is indicated. Fractures of the shaft are treated by malleable-iron fracture splints which can be bent to cover in the shoulder-joint and thus produce fixation. All fractures in the region of the elbow-joint, with the exception of the olecranon, are treated after adequate and complete reduction in the Jones' or full-flexed position; this position cannot be obtained unless reduction is complete. Whether the fracture is supracondylar, T-shaped or intercondylar, one must reduce by traction-extension, supination and hyperflexion. If this latter is not obtained the routine must be repeated until it is, and then the arm must be kept in this position at rest for at least three to four weeks. The author gives warning against passive movements after the

arm is being gradually brought down, otherwise traumatic arthritis and consequent stiffness of the elbow ensue. For this type of fracture the rectangular internal splint should be abolished. Fractures of the head and neck of the radius must be fixed in full supination, otherwise limitation of this movement will certainly result. Fractures of the shaft of both bones require consideration of two important points: first, the shaft of the ulna must be kept straight, and secondly, the curve of the radius must be conserved, as the whole length of the posterior border of the ulna is straight, and on this the curved radius rotates like a bucket-handle. Nearly all neglected fractures of the forearm show limitation of supination, whereas pronation is not defective. Colles's fracture requires complete and adequate reduction before splinting takes place. The Jones method is preferable to the handshaking plan, because the force is applied directly to the bone instead of working through the carpal bones. Twisted fracture splints, adequately padded, to keep the replaced fragments in an overcorrected position and the hand in ulnar deviation, are applied and remain for four weeks, movements of the fingers and thumb being allowed from the first.

---

## PEDIATRICS

---

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

---

**Nephritis in Children.**—Boyd (*Am. Jour. Dis. Children*, 1922, 23, 375) holds that the most common etiological factor in nephritis is an acute infection. Cases of nephritis in childhood may be divided into the following classes: (a) Acute glomerulonephritis, (1) resolving, (2) nonresolving; (b) chronic glomerulonephritis; (c) nephrosis. The acute cases which recover are differentiated from the nonresolving type by (a) a better response to renal function tests; (b) by a steady and rapid improvement clinically; (c) by a rapid diminution and complete disappearance of the albuminuria. The chronic cases differ in the history of past symptoms and signs attributable to the kidney, especially nycturia, in the presence of more numerous casts in the sediment. Relapses recur frequently in the more severe cases and of themselves justify a bad prognosis. Tests of renal function give invaluable aid in determining the prognosis, as well as the line of treatment. The concentration test and the determination of the blood nitrogen constituents furnish the most reliable data. Consideration of the responses to functional tests coupled with clinical observation enables one to foretell fairly accurately the outcome in individual cases. Administration of calcium salts, particularly the lactate, is of definite value in clearing up the edema. Pathologically the most common lesion in the acute cases is a glomerulonephritis of the intercapillary type, accompanied by more or less degeneration in the cells of the convoluted

tubules. The chronic cases showed the same lesions as the acute cases plus searing and fibrotic changes. In the nephrotic cases tubular changes predominated.

---

**The Breast-fed Pellagrin: Relation to the Avitaminoses.**—LUSTBERG and BIRCHETT (*Arch. Pediat.*, 1922, 39, 254) eliminate the specific infectious theory as the causation of breast-fed pellagra. In treating in their institution more than 50 cases a year of men, women and children without segregation there never has developed a case among the other patients or among the help. The manifestations of the disease in both mother and child present themselves in the spring and summer. A dietary error shown to be pre-pellagrous was prevalent in the winter diet of the mother. A pre-pellagrous diet, such as dried beans, dried peas, corn-meal, lard and canned evaporated milk, contains an excess of carbohydrate and lacks protein. This diet is unbalanced and it has excess foodstuffs shown to be poor in vitamins, and further it has not the proteins, a foodstuff which has been shown to be rich in vitamins. The character of this diet undoubtedly influences a baneful effect on mothers' milk, and therefore the suckling infant shares in the deficiencies. Curative results were obtained by placing the infant on artificial food such as cows' milk, fruit juices, vegetables, zweiback and purees. This ration is well balanced and contains vitamins in full force.

---

**Eczema in Breast-fed Infants as a Result of Sensitization to Foods in the Mother's Dietary.**—SHANNON (*Am. Jour. Dis. Children*, 1922, 23, 392) found that eczema in breast-fed babies was a result of sensitization to food proteins contained in the mothers' dietary, and transmitted to the infant through the breast milk in a great majority of cases. Removal of these proteins from the diet of the mother usually results in cure of the condition in the patient. In cases in which all the foods cannot be eliminated from the diet of the mother, limitation of the same will often result in improvement of the eczema, presumably because there is a threshold in the mother up to which the food may be taken without its harmful constituents appearing in the breast milk. Sensitization of the infant may be determined by the cutaneous reaction to the purified proteins. The erythematous reaction at the site of the test is to be considered as indicating sensitization, and being much more common than the wheal, is correspondingly more important. Sensitization is usually multiple, and may be to a majority of the foods in the dietary of the mother. Sensitization to become more widespread in a great many cases as time goes on, due to acquisition of sensitivity to new foods. Repeated exacerbations and failure to cure may be due to a lack of coöperation on the part of the mother, to sensitization so widespread as to make sufficient limitation of the diet impossible, to failure on the part of the physician to test for all foods, to the acquisition on the part of the infant of new sensitization, and to error in the procedure of determining sensitization whether avoidable or otherwise. As general prophylactic measures, it is recommended that all mothers be cautioned to eat a large variety of foods, and a small quantity of any individual article of diet, that eggs be restricted rather than forced in the diet of the mother, and that all cases of eczema be



studied early and that offending foods be eliminated before sensitization becomes so widespread as to make limitation of the diet impossible. The proper study of all cases of eczema in breast-fed babies that do not yield promptly to the older methods of treatment requires the determination of sensitization in the infant to all of the foods contained in the diet of the mother and in the event of exacerbation, the frequent repetition of these tests.

**Sitting Height and Stem Length in Private-school Boys.**—GRAY (*Am. Jour. Dis. Children*, 1922, 23, 406) feels that height measurements are being rivalled and possibly superseded by measurements of the trunk independent of the legs. The best trunk length seems to be the sitting height at present, as well as the stem length. These measurements are closely similar. In his report these two measurements are taken from 114 picked upper-class school-boys. The sitting height was not constantly parallel to the stem length, for while it averaged one-half inch greater it varied anywhere from being identical in some boys to two inches greater in others. The stem length was found to be easier to measure accurately as there were more constant agreements in repeated measurements. The absolute values both of stem length and sitting height, averaged according to age, showed greater values than any that he was able to find in the literature. This is natural considering the advantages enjoyed by this group of boys, as it is certain that strains of men can be bred as well as horses.\* The proportional sitting heights, or sitting heights related to stature, were markedly less than those in the literature. This means that well-developed children have longer legs for their heights than children retarded in growth, which may be stated that the principal defect of growth in badly nourished children lies in the lower extremities. The author believes that stem length should replace the sitting height measurement in the fields of anthropology and of school hygiene.

**Prophylactic and Therapeutic Value of Pertussis Vaccine.**—DAVIES (*Am. Jour. Dis. Children*, 1922, 23, 423) states that pertussis gained access to his institution through a child who had been exposed before admission. Of 176 children exposed, 114 had not had the disease 20 had had the disease, and the history was inadequate in 42 cases. Thirty-three children developed the disease. Records in 27 of these cases were negative for previous attack and doubtful in the remaining 6. These cases were admitted to the hospital ward with a positive diagnosis of pertussis based upon the clinical findings in the majority of the cases. The remaining 146 children were given prophylactic doses of pertussis vaccine regardless of previous history. After the first 33 cases were removed from the main building only 4 additional cases developed. It is quite sure that the others were exposed to the disease at the time of the greatest infectivity. Most of the children were very young, and the majority had not had the disease. Although it appears that the individual child responds differently to the pertussis vaccine, the duration of the disease is shortened by its administration. The paroxysms were lessened in severity and duration, and whooping and vomiting were obliterated.

**The Basal Metabolism of Infants Fed on Dry Milk Powder.**—TALBOT and MORIARTY (*Public Health Reports*, 1922, 724, 176) found that metabolism studies in their series of cases show a tendency for the males to fall within or very close to the standard variations, the greatest deviation being in the calories per kilogram of body weight. The metabolism of the female infants ran higher, and with few exceptions fell more than 10 per cent, the average, but were not outside of the extreme normal variation. This is in accord with the metabolism of the different sexes is in accord with what BELL and Talbot found in their series of observations; that is, that it is much more difficult to predict the metabolism of female than it is of male infants, and that the deviation from the average was much greater in the former than in the latter. The results of the findings of this study on the basal metabolism of infants fed on dry milk powder show either a normal or a slightly elevated basal metabolism. Coincident with most of the cases of an elevated metabolism there was an elevation in temperature to  $99^{\circ}$  or  $100^{\circ}$ , but it does not seem that this slight elevation in temperature is sufficient to explain the increase in metabolism. One case had been vaccinated against smallpox six days previous to the metabolism observation. There are no published data on the effect of vaccination on the metabolism, but it does not seem unlikely that the metabolism would be more likely to be increased about the tenth or twelfth day of the reaction rather than earlier. In these studies all precautions were taken to insure quiet periods, and careful and kymograph records were kept of the infants during the metabolism periods to warrant recording the results as purely basal findings. The basal metabolism of this series of infants fed on dry milk powder mixtures tends to be slightly higher than that of average normal infants, but is within normal limits. This may have been due to relatively high protein content of the food, but the deviations from the average are not great enough to permit any striking conclusions to be drawn.

**Treatment of Pylorospasm in Infants.**—GRULEE (*Jour. Am. Med. Assn.*, 1922, 78, 1183) calls attention to the fact that thick food may cause in infants with pylorospasm a serious febrile reaction followed by symptoms of shock. Because of this he feels that a more physiological method of caring for these patients might be of value. Provided a treatment is effective, its simplicity is a great recommendation. It is frequently necessary to insist on hospital treatment so that the best results may be obtained. There are two indications for treatment of pylorospasm: The first is to relax the spasm at the pyloric sphincter, and secondly to remove the irritation in the stomach resulting from the accumulation of disintegrated food which has remained in the stomach as a result of the pyloric closure for a period longer than the normal. For the first of these conditions the employment of atropine is advised; for the second the cleansing of the stomach and the administration of a food which is adequate but not irritating. In following out these suggestions the author gives atropine hypodermically in a quantity of from 1/1000 to 1/500 grain fifteen minutes before each feeding. Before the food is given, the stomach is carefully washed until the washing returns clear. The food is then given through the tube before it is withdrawn. He nearly always gives a mixture of albumen milk

and a dextrin-maltose combination, a quantity sufficient to meet the needs of a child of like age without gastrointestinal disturbance. In breast-fed babies he allows suckling after the stomach washings. His results in this group of cases is not nearly so satisfactory as in the artificially fed, but he has never felt that it was wise to discontinue breast nursing for this reason. Results appear early and often within two or three days the vomiting ceases entirely, or there is only slight regurgitation. This is followed by a rise in the weight curve. The stomach washings are intermitted and if no relapse occurs, they are finally discontinued and the atropine dosage gradually diminished until it finally reaches zero.

## OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

**Albuminuria in Pregnancy.**—BOURNE (*Brit. Med. Jour.*, April 1, 1922, p. 520) believes that further knowledge concerning albuminuria in pregnancy must be gained by chemical study. Under this title is commonly described a group of symptoms of which the most important is the presence of albumin in the urine; next in importance increased blood-pressure. As far as types were concerned the first and most common is subacute nephritis. The second in frequency is the cerebral type, where convulsions occur in labor, often without premonitory symptoms except the presence of albumin in the urine. The third type which he describes is the gastric type, characterized by uncontrolled vomiting, occasionally seen in early pregnancy. This he considers as really of hepatic origin. The fourth class is the hepatic condition which he finds rare; and the fifth, the so-called uterine type with necrosis of the uterine wall and serious hemorrhage. In 4000 cases of pregnancy and labor, 30 per cent had some degree of albuminuria. Unless high blood-pressure, vomiting or other symptoms develop, albuminuria alone is not important. Convulsions indicate serious danger, and 46 per cent of patients, having albuminuria have convulsions. When these patients do badly, it is in one of three ways; by convulsions or by the complete suppression of urine, due to necrosis of the cortex of the kidney, or by the development of jaundice. The number of convulsions had no direct relation to the mortality. Where patients were suffering from toxic albuminuria, it was especially serious if fresh symptoms appeared during medical treatment, or if the symptoms already present suddenly became intense.

HOLLAND, studying the after-condition of patients who had eclampsia and albuminuria, found that a considerable percentage of them showed signs of chronic kidney damage afterward. He believed that labor should be induced in all such cases.

WALLIS, studying the blood and urine, found that after the fourth

month the blood-urea and blood-sugar were less than in the normal non-pregnant woman. The quantity of diastase was increased. In the toxemia of pregnancy blood changes were slight: Cholesterol was increased, especially in cases of eclampsia; in the urine a high diastase percentage preceded albuminuria. He would distinguish between the toxemia of pregnancy and a true nephritis in pregnancy by the estimation of urea in the blood and diastase in the urine. WILLCOX considered the corpus luteum an important factor in producing toxins. He believed that the toxins produced in pregnancy damaged the organs of excretion in each succeeding pregnancy.

The same discussion before the Harveian Society is reported by the *Lancet*, April 1, 1922, p. 651. In reporting Bourne's paper it is stated that in 18,000 cases of labor at Queen Charlotte's Hospital, but 3 cases of the hepatic form of toxemia have been observed. Eclampsia can occur with comparatively low blood-pressure, as cases are reported where the blood-pressure was below 160 mm. The mortality curve of all toxemic patients was 5 per cent; where the blood-pressure was 150 mm. or below the mortality was 9 per cent; where it was 190 or above, the mortality was 27 per cent. Holland is quoted as stating that at least 12 per cent of eclamptic patients suffered permanent damage to the kidneys.

---

**Pneumonia in the Newborn.**—(*Brit. Med. Jour.*, March 25, 1922, p. 469), BROWNE publishes a paper upon pneumonia in the newborn. In 80 cases of infantile death in the Royal Maternity Hospital, Edinburgh, there were 21 or 26.25 per cent in which the cause of death was found to be pneumonia; 11 were in premature and 9 in full-time infants, the ages varying from eight hours to five weeks. The fact that so many of these cases were premature, shows that the premature infant is especially liable to infection. It is estimated that the premature infant is fourteen times as liable to die from pneumonia as is the infant born at full time. It is also of interest to know that 5 of these infants were syphilitic, another probably so, while 1 had fracture of the supraorbital plates with extradural hemorrhage overlying them. One of the syphilitic cases had an extradural hemorrhage in the spinal cord. Among the premature infants were many with areas in the lungs, where the lungs had not expanded; in some involving part of one lung and a large part of the other. It seems probable that this condition predisposes to pneumonia. There were 2 very instructive cases of premature rupture of the membranes, followed by pneumonia in the infant. In 1 the pneumococcus was present, in the other the *Bacillus coli communis*. One of the mothers was delivered by forceps, and the other had induced labor. Both mothers made uninterrupted recoveries, and evidently the children died from infection, developing before or during birth. Of the pathology of the condition, there were 11 cases of the ordinary catarrhal pneumonia, 1 with pleural effusion, 2 with empyema.

There were 2 cases of interstitial pneumonia with catarrhal pneumonia added. In 1 case of catarrhal pneumonia there was hemorrhage into the bronchial tubes and into the lungs. In 5 cases there was acute congestion and edema of the lungs with hemorrhage into the lung substance. In 1 case there was both interstitial and catarrhal pneu-

monia and hemorrhage, and in 1 interstitial pneumonia with congestion and hemorrhage. The catarrhal pneumonias were in a fairly advanced stage of consolidation. It is sometimes difficult on examining the lung to distinguish precisely between the different varieties.

Among new-born infants pneumonia is a common cause of death during the first week of life, and occurs in 26 per cent of new-born children. It may be caused by infection before birth, following premature rupture of the membrane, and at the time of birth the child may be in an advanced stage of pneumonia. The child has very little defensive reaction against infection as compared with the adult. In the first few days of life pneumonia is an exceedingly insidious disease; generally presenting no characteristic symptoms which might lead to its presence being suspected or established on physical examination. The microscopic examination of the lungs may be necessary, and the postmortem examination in the ordinary manner may fail to make a diagnosis. The acute hemorrhagic pneumonia of infants is a distinct condition. In this condition children, previously apparently healthy, either full time or premature, may die suddenly. This death is preceded by acute congestion of the lungs, followed by hemorrhage from the rupture of fragile blood vessels. Very often sudden death is preceded by nose-bleed, pallor and it is thought that the cause of the accident may be something in the nature of an anaphylactic action. Two precautions are imperative in the interest of new-born children: the avoidance of premature rupture of the membranes during labor and the taking of every precaution to protect the child against infection.

---

**Osteomalacia with Rupture of the Uterus.**—SCHOCKAERT of Louvain (*Gynécologie et obstétrique*, 1922, Tome 5, No. 2) describes the case of a patient aged forty years in her seventh pregnancy, in labor several days. She was brought to the Maternity at Louvain in miserable condition. The history showed the usual diseases of childhood, that menstruation appeared at seventeen and had always been regular. The six preceding pregnancies had terminated normally. Three children were living and in good health; 2 had died; 1 from some affection of the digestive tract, associated with alterations in the bone probably rachitic; the other had died of angina.(?) The patient had been ill three years; before her sixth pregnancy she had suffered from continuous pain in the lower extremities, especially in the thighs and knees. It had become impossible for her to flex the leg upon the thigh and the thigh upon the pelvis. Later, pain developed among the lower ribs and this became so excessive that the patient made no effort to speak or laugh, and finally pain became severe in the region of the symphysis pubis. Little by little the whole skeleton with the exception of the bones of the cranium had become painful. The patient was pregnant, and during the pregnancy she had grown rapidly worse, to a degree that she could not walk on account of her suffering. Her labor had taken place spontaneously without medical attention and the child had been born alive and survived. After the birth of this child the patient still suffered with pain and could not move without assistance. She remained in that condition until the beginning of the present and succeeding pregnancy. From the history it seemed evident that the physician who had been called to treat her had considered her to be

suffering from rheumatism. This was exceedingly unfortunate, for if the ovaries had been promptly removed at this time, the progress of the disease might have been checked. At about the third month of the seventh pregnancy the patient was unable to walk. Pain became almost intolerable. Her pregnancy continued however, until she was practically at term. She was without medical attention and supposed to be suffering from rheumatism. Three or four hours before she was brought to the Maternity her labor pains began and increased steadily in intensity. The patient could not describe accurately what had happened, and the third day she called a physician, who examined her and ordered her sent to the hospital. On admission the patient was desperately ill, with pulse 140, frequent and shallow breathing and temperature 102° F. She suffered intense pain when touched on any part of the body. The abdomen was enlarged, the uterine tumor falling toward the right. It was difficult to make out the child, but the back seemed to be in front, the head towards the left flank. The different fetal parts seemed to be very superficial. No heart sounds were present and examination suggested that the uterus had ruptured. On attempting to make a vaginal examination it was discovered that the pelvis had assumed the characteristic shape of osteomalacia. The rami of the pubes were very close together; the sacrum was projecting and curved; the cervix uteri was soft and the placenta could be felt, but no fetal part. Exuding from the uterus was a brownish bloody fetid fluid. Abdominal section showed blood in the abdomen, amniotic liquid and a dead fetus lying among the intestines. The placenta was still in the uterus and the uterus had ruptured. Apparently this had occurred at least two days before. The child was somewhat macerated. A Porro operation was rapidly done and a strand of gauze passed for drainage through Douglas' cul-de-sac. The patient did not long survive the operation.

---

## GYNECOLOGY

---

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY  
OF PENNSYLVANIA, PHILADELPHIA.

---

**Histogenesis of Ovarian Tumors.**—The question of the histogenesis of ovarian epithelial tumors, both solid and cystic, has been the subject of much discussion. In view of the wide variations in opinions any evidence that will at all tend to help in the classification of these common and clinically important tumors and that may tend to indicate their origin is of sufficient value to make a record of it, as has been done by Geist (*Am. Jour. Obst. and Gyn.*, 1922, 3, 231). His studies are

based upon a patient, fifty-two years of age, in whom the ovary on one side presented a typical adenocarcinoma and on the other side a process involving the greater portion of a somewhat enlarged ovary that also resembled a new growth. It is composed of masses of cells, varying in number, either isolated or in large branching strands. The cells in these solid masses resemble the granulosa layer of the follicle. In these masses are found cysts of varying sizes lined by cells of a cuboidal, columnar or the high cylindrical type as seen in the pseudomucinous type of ovarian cyst. Often in these cysts are found oval granular bodies which on superficial examination might be taken for degenerated ova but which are undoubtedly degenerated tumor cells or secretion masses. The origin of this process is the point of interest. It seems to be independent of the tumor of the other side, first, as it bears no histologic resemblance to it, and, second, as it has none of the distinguishing criteria of a malignant tumor. The stroma resembles that of the unchanged ovary and is a predominant part of the process. The stroma and cells always maintain a definite relationship and at no point is there a proliferative or invasive tendency or an inflammatory infiltration. Mitoses are not found. The cells composing the tumor resemble in their appearance and arrangement the granulosa cells and the general structure of the growth in parts suggests the developing follicle with many variations. Because of this morphologic appearance, the arrangement of the tumor and the wide variation in its structure it is suggested that a cell of great potentiality must play the role of originator. In addition, the development of cysts which form by degeneration of the larger cell masses and grow by coalescence suggests this as one method of development of the microcysts and later of the larger cysts that occur in the ovary. Furthermore, the cells lining these cysts are often cuboidal, and occasionally high, cylindrical, mucin-containing elements can be traced by direct observation from the large cell masses of granulosa-like cells. This leads Geist to the presumption that some of the so-called simple cysts, follicular cysts and even the more complex pseudomucinous cysts may be the products of these same embryonal remains. The nomenclature employed for the classification of this type of tumor is still indefinite, as each writer has selected a name that has fitted his theory of origin or the fancied resemblance to some structure of the ovary. At the present time there are tumors similar to the one above described that have been termed adenoma of the Graafian follicle, folliculoma malignum, carcinoma folliculoides, oöphoroma folliculare and folliculoma. Several of the names can be discarded, such as adenoma of the Graafian follicle, folliculoma malignum and carcinoma folliculoides, as the tumor is neither a malignant tumor nor an adenoma. Geist believes that the best way to classify these tumors is not to give them a name but to group them as tumors arising from persistent embryonal structures.

---

**Hemorrhage from Ruptured Corpus Luteum.**—Intraperitoneal hemorrhage may arise from various sources, most often from a ruptured ectopic pregnancy. Aside from hemorrhages of a purely traumatic origin, such as ruptured liver, kidney, spleen or pancreas, spontaneous rupture of the uterus may be mentioned. Very rarely, exceedingly serious intra-abdominal hemorrhage occurs, traceable to none of these

sources, but either to a ruptured Graafian or atretic follicle or to a ruptured corpus luteum. A survey of all the available literature on intra-abdominal hemorrhage from ruptured corpus luteum impressed MOORE (*Ann. Surg.*, 1922, 75, 492), who reports such a case, with the fact that in none of the cases reported, so far as he had been able to ascertain, was the correct diagnosis made before operation. The reason for this is quite apparent: intra-abdominal hemorrhage following rupture of the corpus luteum is a rare occurrence compared with the other pathologic conditions which present an almost identical picture, and it is only natural that the diagnosis which most often fits a condition should be the one made. In general the reports show that the symptomatology of this condition is characterized by sudden abdominal pain, cramp-like or colicky, followed almost always by nausea and vomiting. There is nothing characteristic about the temperature and pulse. Localized abdominal pain and tenderness, generally on the right side, are noted almost immediately after the onset of the sudden pain. Frequently abdominal rigidity and distention are present. The patient is pale, but seldom seems to be in shock. While these symptoms in a woman are characteristic of trouble in either the appendix or Fallopian tube, the possibility of a hemorrhage from the ovary must be considered, especially if the patient shows a marked degree of pallor or anemia. If the menstrual history has been normal and if the patient has had previous intestinal disturbances simulating appendicitis, it is quite natural that a preoperative diagnosis of acute appendicitis should be made. As soon as the abdomen is opened and it is found to be filled with blood, the surgeon decides that the case is a ruptured tubal pregnancy. A rapid search, usually through a right rectus incision, fails to locate bleeding from either tube. Further examination shows the bleeding to be coming from the ovary. Sometimes the condition is complicated by the presence of acute or chronic appendicitis, but often the appendix is found to be normal. The ovary should be considered an aggregation of follicles, some maturing and some retrogressing, constantly changing their appearance and function from day to day. The structures surrounding the different follicles also change, depending on the development and special function of the follicles. The ovarian stroma with its nerves and bloodvessels forms the framework for housing these follicles. Each follicle seems to have a life cycle of its own. All appear alike during their early development, but each month one gradually outstrips the others in growth and develops into a Graafian follicle. Whether this follicle is always different from the others, or whether because of its richer blood supply it grows faster, is not known. At any rate, the ovum of this largest follicle, called the Graafian follicle, is the only one which matures and when ripe is extruded. As soon as this takes place there is no further growth of the other follicles which started to mature; their ova die and gradually disappear, leaving the so-called atretic follicles. Only one ovum grows to maturity each month. Following the giving off of the ovum great changes occur in the Graafian follicle, producing what is known as the corpus luteum. The maturing follicle receives its blood supply from vessels in the theca interna, from which tiny offshoots penetrate into the granulosa. The earliest stages of the corpus luteum are marked by a great increase in the number and size of these vessels in the theca and also at the base of



the granulosa. This fact is of particular interest, since it seems to indicate that, due to the stage of hyperemia which follows extrusion of the ovum, hemorrhage can occur more readily into a corpus luteum than into a Graafian follicle. To the physician who has not seen an abdomen filled with blood exactly as it is found during a ruptured ectopic pregnancy, it does not seem possible that such an extensive hemorrhage could come from the tiny vessels which encircle the follicles, but this has been proved on numerous occasions by surgeons who have actually seen the blood coming from the ovary and also in some instances by microscopic sections which demonstrated the origin of the bleeding.

**Prognosis of Cancer of the Cervix.**—SKEEL (*Am. Jour. Obst. and Gyn.*, 1922, 3, 252) has made a collective review of the statistics relative to cancer of the cervix from numerous clinics, and after a thorough digestion of his material he states that two things stand out with increasing distinctness: First, the mortality rate from operation goes down with increasing experience. Thus many writers refer to their last 30 or 50 or 100 cases when stating the possibilities inherent in the Wertheim operation. Second, the operative recovery rate and freedom from recurrence are enormously increased by early diagnosis and early operation. Though the data do not justify so high an operability rate, so low a general mortality rate, nor so high an absolute curability rate, he presents in round numbers what has happened at the expiration of five years to 100 women with cancer of the cervix, if 50 per cent were operable. There would be only a 10 per cent mortality rate and there would be 20 per cent of absolute cures. Out of 100, 20 would be well, 50 inoperables would have died, all presumably having had a Percy cauterization, or some other form of local treatment; 5 of the 50 operated upon died at once and the remaining 45 died from a recurrence. Of the 50 who underwent a tremendously severe operation, 30 were dead within five years. Were the operation less serious, less heroic, and less frequently complicated by postoperative sequelae, such a showing might be justified; but with the reverse true, the author believes that it lacks justifiability when performed upon the present indications of operability. He concludes that any expectation of an increased number of cures of cancer of the cervix by surgical methods must be based upon earlier diagnosis and panhysterectomy should be reserved for cases in which a positive diagnosis can be made only with the microscope. The parametrium being free so far as digital examination can determine, but the case being far enough advanced to be diagnosed clinically, a high cautery amputation of the cervix, followed by radium treatment, offers the greatest hope of cure. The advanced surgically hopeless case should be treated, according to the author, by radium rather than with the knife, curette or cautery, chemical caustics or Percy cauterization, unless profound toxemia or serious infection contraindicates local interference of any kind.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

**A Study of the Gonococcus and Gonococcal Infections.**—With the idea of devising improved methods of diagnosis in gonorrhea and of determining whether typing of strains of gonococci could be made, COOK and STAFFORD (*Jour. Infect. Dis.*, 1921, 29, 561) performed various investigations with stock cultures of gonococci, attempted to isolate fresh cultures from acute cases of anterior urethritis in men and chronic cases in women, and conducted certain immunity tests in gonococcal infections. The stock cultures of gonococci were found to grow satisfactory for routine work on testicular agar, while chocolate blood testicular agar proved to be useful for increasing the vitality of a weakly growing culture. Increased atmospheric moisture but not a reduced oxygen tension were environmental requirements of the organism. Isolation of cultures from acute cases of anterior urethritis in men was most successfully accomplished on chocolate blood testicular agar. No pure cultures of gonococci were obtained from chronic cases of gonorrheal endocervicitis, although single colonies were found on plates of hydrocele testicular agar containing certain members of the triphenyl methane series. The complement-fixation test served only as an aid in diagnosis, being considered by the authors as confirmatory evidence rather than as an independent basis of diagnosis. It was of little value in early cases. A nonspecific reaction was obtained on the intracutaneous injections of a preparation of gonococci. No typing of strains followed the use of complement-fixation and agglutination reactions or by means of the method of absorption of agglutinins.

**Absorption from the Peritoneal Cavity.**—BOLTON (*Jour. Path. and Bacteriol.*, 1921, 24, 429) conducted extensive observations on the mechanical and physical factors concerned in the process of absorption from the peritoneal cavity of cats, paying especial attention to the paths by which the absorption is accomplished. That there was a total and uniform rate of absorption of fluid from aseptic cats was determined by injecting it into normal cats and observing the quantity remaining at varying intervals, along with the concentrations of solids. By the use of such colloidal dyes as Congo red, eloth red and Congo blue it was found that each diffused directly into the bloodvessels, but at a slower rate than in the case of crystalloids. In studying the lymphatic paths of absorption, by injections of colloidal silver, it was found that the anterior mediastinal lymph glands were first to be stained, as were the diaphragmatic lymphatic channels. The lumbar lymph glands became

stained later and to a lesser degree. By introducing a suspension of lamp black in 0.9 per cent salt solution and controlling the respiratory movements by bleeding or asphyxia, it was noted that the rate of passage of the particulate matter into the thoracic lymphatics was *proportional to the violence of respiration*, the absorption being purely mechanical and commencing at once. Sarcina and staphylococci passed through the diaphragm in smaller quantity than the lamp black but were scattered uniformly about the periphery of the lymph glands in fair numbers. The author concludes, in part, from his investigations that "the peritoneal cavity is drained principally by the diaphragmatic lymphatics into the mediastinal lymphatics passing through the sternal and anterior mediastinal lymphatic glands to the right lymphatic duct, and also through anastomoses in the chest to the thoracic duct. It is drained also by the diaphragmatic lymphatics into the cisterna chyli, but this path is quite subsidiary to the former. It is probably also drained to a small extent very slowly by the retroperitoneal lymphatics into the cisterna chyli."

---

**Diphtheria Carriers among Massachusetts School Children.**—BECKLER, GILLETTE and PARKER (*Jour. Infect. Dis.*, 1921, 29, 577) found only forty-one (0.49 per cent) positive cultures of diphtheria bacilli in the nares and throats of 8389 five- to fifteen-year-old school children residing in thirty-five cities in Massachusetts. The cultures were planted on Loeffler's blood serum (Ph 7.2), and after fourteen to eighteen hours' incubation at 34° C. smears were stained with Loeffler's methylene blue and examined by the same bacteriologists. The highest percentage of positives in any one group was 13, when four positives were encountered in thirty-one cultures from one school room. Of the thirty-eight cultures on which virulence tests were conducted, all but two (95 per cent) were virulent, killing unprotected guinea-pigs in from forty-eight to sixty hours. Many diphtheroid bacilli were encountered during the examinations. In 1915 the same investigators obtained positive cultures in only 0.6 per cent of over 6000 contacts.

---

**Presence of *Bacillus Lactimorbi* in the Throats of Cats.**—Having shown previously that *Bacillus lactimorbi* occurs in the human throat, and indicated the danger of its confusion with *Bacillus diphtheriae* and having also indicated the danger of its confusion with *Bacillus diphtheriae*, PERKINS and SHEN (*Jour. Infect. Dis.*, 1922, 30, 505) examined cultures from the throats of twenty-two cats in view of the recent reports inferring that these animals may be carriers of diphtheria bacilli. Swabs were taken from the noses and throats, planted on blood serum, incubated for eighteen hours at 37° C. and stained for granules. All apparently positive cultures were then heated in suspension for ten minutes at 80° C. and inoculated on glycerol agar. By this method the non-sporeforming organisms were killed. In examining smears from the second (glycerol agar) cultures, *Bacillus lactimorbi* was found in two out of the twelve cats in the first series and in five out of the ten in the second series. The authors again emphasize the danger of confusing *Bacillus lactimorbi* with *Bacillus diphtheriae* and hope that their results will stimulate investigators in other parts of the country to ascertain whether this group of bacteria is common to all the states.

**Is Cancer Mortality Increasing.**—"To determine whether or not there is a real increase in cancer mortality we must compare cancer death rates for the same ages, since cancer is an old-age disease." Accordingly STRONG (*Jour. Cancer Research*, 1921, 6, 251) quotes some statistics as compiled from the records of several large insurance companies. The experience of two of these companies covering the eleven-year period from 1911 to 1921 inclusive indicates, taking the figures at their face value, that for ages below sixty-five there is either a fluctuating or a slightly decreasing in cancer mortality, while for the ages sixty-five and over there is probably on the whole some increase. Meanwhile the statistics of the United States Registration Area show a continuous increase in cancer deaths. These are population statistics, however, and are not analyzed as to ages. As these deductions are from statistics one should not forget, before accepting them as final results, that certain circumstances and considerations might modify them. Certainly there has been a gradual increase in correctness of diagnosis, so that in the past many deaths attributed to old age and other diseases should properly have been ascribed to cancer, with the result that if there were a really stationary cancer mortality it would appear to be increasing considerably. The author believes "that we cannot now determine whether the cancer mortality is slightly increasing, practically stationary or slightly decreasing, but that we can be sure it is not greatly increasing." He also says "that such a conclusion does not lessen at all the seriousness of the cancer problem."

---

**Studies on the Formol and Wassermann Reactions.**—ARMANGUÉ and GONZALES (*Jour. Infect. Dis.*, 1922, 30, 443) have been able to confirm the findings of Pauzot and of Ecker as differing from the results obtained when formol was added to sera according to the method described by Gaté and Papacostas. The technique as applied by these authors differed from the original only in that readings were made after a lapse of forty to forty-eight hours instead of twenty-four to thirty hours. Of 41 cases which were strongly positive by the Wassermann reaction only 11 were positive by formol, 4 were doubtful and 26 were negative. Just 1 was positive, 1 doubtful and 4 negative by formol in six instances where the Wassermann was weakly positive. In 127 cases where the Wassermann was negative, 5 showed positive, 1 doubtful and 121 negative by the formol method. On the other hand positive formol reactions were obtained in 67 per cent of cases of malignant tumors which yielded negative Wassermann reactions, a higher percentage than among the syphilitic patients. The sera of pregnant women (seven to nine months) always gave a negative formol reaction. Sera of dogs, rabbits, guinea-pigs, hogs, etc., were uniformly negative, but positive tests occurred in tenia infestations of dogs, in rabbits with eoeidiosis and in a rabbit with hydatid cysts. It was found that formol positive serums were rendered negative by dilution with water to more than 1 to 5 and 1 to 6. The authors conclude "that the formol reaction was not due to some specific substance but to a relative increase of the usual constituents of normal serum, possibly globulins."

## HYGIENE AND PUBLIC HEALTH

---

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

---

**The Behavior of Cultures of Chick Embryo Tissue Containing Avian Tubercle Bacilli.**—SMITH, WILLIS and LEWIS (*Am. Rev. Tuberc.*, 1922, 6, 21) state that tissue cultures afford a means by which the behavior of living cells toward living tubercle bacilli can be followed under experimental conditions which are not greatly injurious to either form. Such observations have shown that: (1) Tubercle bacilli were taken in by clasmatoocytes, fibroblasts, white blood cells, endothelial cells, mesothelial cells, ectodermal cells, liver cells, kidney tubule cells, and cells lining the bronchioles and alveoli of the lungs. No microorganisms were observed in red blood cells, striated muscle cells, nerve cells or ciliated epithelial cells. (2) The phenomena accompanying the appearance of tubercle bacilli within these cells were precisely the same as those shown by similar cells in regard to other foreign bodies. Entrance into cells was dependent upon the consistency of the cytoplasm of the cell, the composition of the foreign body, and also the position of the foreign body in relation to the surface of the cell. (3) Contrary to the generally accepted idea, the cell did not make any active movements toward the bacillus, nor was any migration of bacilli toward the cell observed. (4) The number of microorganisms taken in by the cell and the rapidity of the process varied greatly with the different types of cells. The clasmatoocytes were the most active; after that, the giant cell, the non-granular white blood cell, the granular white blood cell, and the fibroblast, in the order named. (5) Once inside the cell, the bacilli were moved back and forth in the cytoplasm in a manner characteristic of included foreign bodies. In course of time a small vacuole formed about the microorganism, which was eventually destroyed. (6) The presence of tubercle bacilli within the cell or in the explant did not stimulate the formation of giant cells. The emulsion injected into the peritoneum of pigeons produced progressive disease of moderate severity.

---

**Experimental Studies on the Etiology of Typhus Fever.**—OLITSKY (*Jour. Exp. Med.*, 1922, 25, 121) presents experiments to show that the typhus virus in the tissues of the guinea-pig during the height of reaction to the experimental disease does not lose its infecting power when the cells of the brain or of the spleen are disintegrated by repeated freezing and thawing, or by freezing and desiccating, or by crushing by mechani-

cal means, or by grinding into a homogenous pulp with sand. He states that the virus after such treatment is as actively infective as in the same tissue not subjected to the disintegrating influences. The possibility exists, therefore, of an extracellular condition of the typhus virus. Fourteen attempts to filter through Berkefeld V and N candles the virus contained in the disintegrated tissue have all resulted in failure.

---

**The Bacteriology of the Blood of Dogs with Eck Fistula.**—As "there is an impression, supported by considerable evidence, that organisms from the bowel often enter the portal stream and in the liver are effectively disposed of," DAVIS and MATHEWS (*Jour. Infect. Dis.*, 1921, 29, 313) conceived the idea that proper conditions to test this point might be furnished by Eck fistula—that is, an artificial communication between the portal vein and vena cava with the portal vein ligated above the anastomosis just at the hilus of the liver. The experiments were performed on Eck fistula dogs and consisted in taking blood cultures at varying intervals after the operation, as well as after the introduction of *Bacillus pyocyaneus* and *Bacillus subtilis* into the stomach and *Staphylococcus albus* into the venous circulation. All experiments were controlled by similar observations on normal dogs. It was found that in dogs with Eck fistula, bacteria do not appear in the circulation in any appreciable numbers; that Eck fistula dogs are no more susceptible to infection of lungs or of the other organs than are normal dogs and that microorganisms disappear from the circulation as rapidly in dogs with Eck fistula as in normal dogs.

---

**Experimental Streptococcus Pneumonia and Empyema, III.**—Having previously produced experimental Streptococcus empyema in rabbits by direct injection into the pleural cavity of very small amounts of a passage strain of *Streptococcus pyogenes*, GAY and RHODES (*Jour. Infect. Dis.*, 1921, 29, 217) have repeated, experimentally, what is presumably the entire life history of this form of infection in man and have been able to furnish light on its exact course. By means of a soft rubber catheter pushed down the trachea amounts of culture varying from 0.01 up to 10 cc were insufflated into the bronchi of 18 rabbits. All developed bronchopneumonia followed by empyema. It was found necessary to force a small volume of air into the lungs after the streptococcus culture had been introduced into the trachea through the catheter. Similarly, pneumococcus (Type I) cultures were injected intrabronchially into a small series of rabbits. The microscopical findings in the involved areas were quite distinct from the lesions produced by the streptococcus. Death was due to a septicemia which was only irregularly encountered in the streptococcus infections. In the streptococcus infections the pneumonia is lobular in distribution, necrotizing in effect, does not resolve readily and is characterized by peribronchial and perivascular edema and later infiltration of mononuclear cells, being different from the pneumonia produced by the pneumococcus. In the streptococcus infection, pleurisy with effusion occurred, involving by extension both pleural cavities and the pericardium. It was found that the natural route of infection with the streptococcus seems to be from alveoli to pleura, rather than by the

lymphatics of the larger bronchi. Inasmuch as when injections are made into the pleural cavity the bacteria never penetrate through the pleura into the pulmonary tissue, the authors believe this would militate against the idea of a lymphatic stream from pleura to hilum. Experiments with an artificial respiration chamber seemed to indicate that the streptococcus passed from the lungs to the surface of pleura in a few minutes. The authors state that "it is evident, however, that conclusions derived from such experiments cannot explain conditions in the living body where it is found that involvement of the pleura takes place in a matter of hours (six to twelve) rather than minutes."

**Negri Bodies in the Salivary Glands and Other Organs in Rabies.**—JACKSON (*Jour. Infect. Dis.*, 1921, 29, 291) examined the salivary glands from 18 rabid dogs and, as controls, from 15 normal dogs. It was found that fixation in Zenker's fluid and staining paraffine sections with alcoholic eosin and methylene blue gave the most satisfactory results. After a careful study, the author concludes that the salivary glands offer favorable conditions for the growth of certain protozoa, some of the developmental forms of which render differentiation between them and certain forms of Negri bodies impossible, or at least a very difficult task. It seemed certain, however, that in many cases of rabies, Negri bodies could be identified positively in the salivary glands. In one dog, sections from all the viscera were examined, Negri bodies being recognized in the brain and the adrenals, where they occurred in the cells of the medulla. Smear preparations of the saliva from rabid dogs failed to reveal the presence of Negri bodies.

**Virulent Treponema Pallidum Recovered from a Stillborn Infant After Twenty-six Hours.**—HAYTHORN and LACY (*Jour. Infect. Dis.*, 1921, 29, 386) call attention to the fact that the *Treponema pallidum* occasionally retains its virulence for some hours after the death of the host—a fact which is not generally recognized and they believe a new observation. They were able to recover pathogenic, motile treponema from a stillborn infant twenty-six hours after its delivery. Great numbers of the treponema were seen by dark field illumination in the serum from superficial skin blebs and from crushed lung tissue. Rabbits which were inoculated intratesticularly with the material developed the typical lesions of experimental syphilis. The authors feel that the well preserved state of the fetus went far to explain the retained virulence of the treponemas which it harbored and stress the fact that the chance of accidental infection from careless handling of syphilitic tissue is not as remote as is generally supposed.

---

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only with the distinct understanding that they are contributed exclusively to this JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

DR. JOHN H. MUSSEY, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

SEPTEMBER, 1922

---

ORIGINAL ARTICLES.

INFECTION OF THE GASTROINTESTINAL TRACT IN SYSTEMIC  
DISORDERS:

MEDICAL VIEWPOINT WITH SPECIAL REFERENCE TO CLASSIFICA-  
TION OF CASES; THE IMPORTANCE OF ADVANCED BACTERI-  
OLOGY AND BIOCHEMISTRY.\*

BY G. REESE SATTERLEE, M.D.

NEW YORK.

THERE is no such thing as a "medical case" in gastrointestinal diseases. Every patient should be studied by the internist and surgeon conjointly. Most cases need minor surgery of some sort, but few need major abdominal operations. Infection plays an important role in every case. The profession is fortunately awakening to the necessity of a very complete survey of every chronic intestinal invalid. Without this thorough study, reports and statistics are without value. In the past, and still unfortunately in the present, many an abdominal operation for gall-bladder disease, stomach or intestinal ulcers, adhesions, chronic appendicitis, bowel resections and exclusions has had bad sequelæ or at least disappointing results. The reason for this has been due, in numerous instances, to overlooked focal infections or to a disregard to the fact that the abdominal pathology may itself constitute a focal infection and require further investigation.

It has long been known that mouth disease breeds stomach and intestinal disorders, but in spite of this fact the mouth has

\* Read before the New York County Medical Society, at the New York Academy of Medicine, December 23, 1921.



been constantly neglected as an important factor in these ailments. The tendency is quite general to regard the mouth as of secondary importance. Even if so considered it must be conceded that focal infections in the mouth or elsewhere may be a detriment to health and should be thoroughly removed. It is our opinion that these focal infections should be removed when practicable, prior to abdominal operation.

The study of the morphology and function of the gastrointestinal tract has made very rapid strides during the past few years. It is now regarded as a routine procedure always to be employed in the investigation of a chronic digestive disorder, no matter how simple the conditions may appear. Morphologic defects in the gastrointestinal tract should be studied from the bacteriologic standpoint. When the stomach or duodenum are involved, cultures from contents removed through the duodenal tube, according to the fractional analysis method, are frequently of value, not alone for diagnosis but for vaccine therapy. Cotton and Satterlee<sup>1</sup> have noted the high bacterial content in gastric contents that are deficient in free hydrochloric acid and also the converse. After a course in autogenous vaccine or serum therapy, the gastric contents have in many instances returned to normal. It is probable that gastric infection has been responsible for the abnormal gastric contents. Our results have made us believe that the bacteria recovered in this way may not be accidental although the method of obtaining the bacteria is necessarily open to criticism.

A large number of causes of gastric and duodenal ulcer are given, Smithies<sup>2</sup> cites 10 causes in 522 cases of proved gastric ulcer. In his list of causes he places only 33.1 per cent under the head of acute and chronic infections. However, it seems reasonable to suppose that there is present infection in the ulcer, at least as a secondary occurrence. Smithies recognizes this. Until we have more definite information as to the origin of these ulcers, we must be contented in dealing with them as terminal affairs in the hope of curing them as such with little chance of prevention.

**The Medical Treatment of Chronic Intestinal Toxemia.** This consists of diet, massage, hydrotherapy and vaccines or serum.

The diet consists of animal protein free food, principally vegetables, fruit and cereals.

Refined white flour is eliminated and whole wheat flour substituted.

The diet at first is very strict; no eggs and very little milk being allowed.

Bran is an essential article and is given once or twice daily—1 to 2 ounces.

<sup>1</sup> Fractional Gastric Analysis, Tr. Section on Gastroenterology and Proctology, Jour. Am. Med. Assn., 1920, 29.

<sup>2</sup> Jour. Am. Med. Assn., 1920, 74, 1555.

When the stools are dry and hard, agar is given in the food.

A liberal diet is permitted and encouraged, but it is often wise to underfeed rather than overfeed.

All laxatives and cathartics are forbidden. This includes mineral oil. Castor oil is useful occasionally when specially indicated, but only under special instructions. The same is true of enemata and colon irrigations.

Continued use of drugs and irrigations is harmful. Colon massage is of great value in obstinate constipation. Its use should be systematic.

Hydrotherapy, in the shape of eliminating cabinet baths, followed by Scot's douche helps the physical welfare of the patient.

Electrotherapy and mechanotherapy are also of great value, provided the patient can afford the time.

*Vaccines and Serotherapy.* It must be constantly borne in mind that the constipation in most of these cases is of toxic origin, probably protective. It is possibly for this reason that laxatives and cathartics are harmful.

It is with this idea in mind that we have practised vaccine and serotherapy in nearly all our suitable cases, and with satisfactory results. Dr. Cotton has found that vaccines and sera are important aids in the treatment of toxic psychoses, both before and after operation. He and the writer<sup>3</sup> practised successfully along these lines before knowing of the other's results. We also had many satisfactory results with the vaccines alone before becoming convinced of the necessity of removing all obvious foci of infection.

The routine procedure for colon vaccines is to obtain the stool after a purgative dose of castor oil. The third stool is preferable, as it contains the virile bacilli from the ceco-colon region. Cultures are taken and a vaccine made from the isolated colon organisms by the usual well-known technic. These vaccines are given as a routine every four days in doses of from 100,000,000 to 300,000,000, depending upon the general reactions. The duration of treatment depends upon the degree of immunity established in the individual case.

*Serum Therapy.* We owe the serum to Dr. Cotton's researches. It is obtained from a horse that has been immunized by the various strains of streptococci and colon bacilli obtained from cultures from infective foci in the patients at the New Jersey State Hospital.

My own results with this serum have been very gratifying in the few cases in which it has been used. The dosage begins at 1 cc and gradually increases up to the full dose of 10 cc.

The one disadvantage of the serum is the occasional occurrence of serum sickness. The intestinal toxic symptoms subside rapidly after its administration.

<sup>3</sup> Satterlee, G. R.: New York Med. Jour., 1918, 107, 971.

Of other therapeutic agents generally employed there is little to recommend. Lactic acid cultures are of little value. Bulgarian bacillary milk has the value of a good milk food and may be of service in some cases.

Saline cathartics are harmful. The intestinal antiseptic drugs recommended, such as salol, creosote, etc., may be of temporary value, but symptomatically alone. Antacids and acids are often necessary and valuable aids, but in final analysis materia medica falls down as a curative agent.

Metabolic studies are essential in some patients in which disorders in metabolism are suspected. The diet should be modified to suit the case.

Infections with their consequent toxemias play the important role in most disorders of the alimentary canal.

If Rosenow's<sup>4</sup> work on the experimental production of gastric and duodenal ulcers following the injection into animals of bacteria derived from cultures from the apices of infected teeth, thereby demonstrating the selective action of bacteria, is as accurate as it appears to be, the value of preventive dental surgery will have been established. Bumpus and Meisser<sup>5</sup> have recently produced in animals streptococcic kidney lesions from cultures obtained from apices of devitalized teeth in patients showing pyelitis at necropsy. Our clinical experience seems quite in sympathy with this theory of the selective action of bacteria, so much so that we use it as a working premise. This lead follows directly into a most important field, that of *preventive surgery of the mouth*. This new and important branch of preventive medicine is still in the experimental stage, and after the necessary adjustments which will follow upon its extended clinical use, will in our opinion, prove to be of very great value. The question of the day is, "Should this problem be left alone to the laboratory worker or developed both clinically and experimentally? Should we leave these badly necrotic areas alone if no local or positive systemic symptoms exist or should we interfere?"

There is great need for more experimental work, and especially for *coöperation* between the oral surgeon, the dentist, the physician and the surgeon.

The bacteriology of dental and oral infections is studied in the laboratory of our office, cultures being taken from the apices of extracted teeth, necrotic bone areas and opened antra and from all tonsillar tissue removed. The technic employed is that of Holman.<sup>6</sup>

The all-important question relates to the effect of these hidden

<sup>4</sup> Jour. Infect. Dis., 1915, 17, 219.

<sup>5</sup> Jour. Am. Med. Assn., 1921, 77, 1466-1468.

<sup>6</sup> The Classification of Streptococcus, Jour. Med. Research, 1916, 34, 377.

chronic infections upon the general mental and bodily condition and on the gastrointestinal tract.

There is every reason to consider the gastrointestinal tract from the lips to the anus as one organ, the structure, development and function being correlated in the closest possible manner. Foci of infection in the mouth or in the rectum frequently give rise to a similar train of symptoms, the predominating ones being constipation and flatulence. The removal of these obvious foci, provided the remainder of the tract is free from focal infection or permanent changes, will frequently clear up the intestinal symptoms and restore, without further intervention, the physical and mental equilibrium.

It is unfortunate, however, that patients are not studied in many instances before the infection has progressed to the stage of gastrointestinal ulcers, gall-bladder disease and permanent changes in the colon, when major instead of minor mutilation is definitely indicated—often with poor results. It is not amiss to speak here of our experience in chronic appendicitis. In a previous paper by one of our group (Satterlee<sup>7</sup>) 25 per cent of the patients with diseased colon had had the appendix previously removed without benefit or with apparent detriment. It is difficult to say just what this means. We incline strongly to the belief that often the primary infection was oral and that by the time the appendix was removed the toxemia had become generalized. When this had taken place the patient's condition was involved and the chances of cure more remote than in the early stages.

From a detailed study of over 1000 chronic intestinal invalids medically treated and of over 200 similar patients in whom a portion or all of the colon had been removed, we have come to the belief that many of these advanced cases with infected colons will not get well until the diseased portion of the organ is removed together with every other local focus. Medical treatment with vaccines and sera is indicated in every case.

The sequence in infective processes of the gastrointestinal tract is difficult to follow and to explain. The infection must travel in one or more of three ways: In the blood stream, lymphatics or lumen of the gut. Our operative experience combined with pathologic and bacteriologic findings leads us to believe that infection from the cecocolon reaches the body cavity *via* the lymphatics, as evidenced by the enlarged lymph nodes in the mesentery. Colon bacilli and streptococci are frequently obtained from cultures of these nodes. Many observers consider that infections of the kidneys and other parts of the urinary tract originate in this manner.

The protective lymphatic system acts as a barrier to bacteremia from these organisms, many of which are very pathogenic.

<sup>7</sup> Chronic Appendicitis and Chronic Intestinal Toxemia, New York, Med. Jour., 1916, 104, 882.

Chronic intestinal invalids, therefore do not suffer from a bacteremia but from a *toxemia*. This debilitates and deteriorates but rarely kills the patient directly. The human system may, under these toxic influences, undergo a lowering of resistance and become susceptible to other and perhaps more lethal infections.

It has become my fixed belief from prolonged study of chronic intestinal toxemia that the colon bacillus, perhaps the pathogenic forms only, is the primary cause of this lowered resistance, and that other types of bacteria, notably the streptococcus, are secondary infections. On the other hand, Bumpus and Meisser, in describing infection of the kidney by the colon bacillus, have suggested that the primary cause of this infection may be streptococci carried to the kidney from the colon through the lymphatics and that the colon bacilli as a secondary implantation have overgrown and supplanted the former. Much more study in the line of clinical research and experimentation is needed in this direction.

My own view of this subject is based on the study of over 500 cases of chronic intestinal toxemia treated by autogenous colon vaccines obtained from stools after catharsis. A suitable case, one with symptoms and signs of a chronically diseased ceco-colon, will invariably improve after the administration of autogenous colon vaccines, and also, as we have discovered lately, of an anti-colon and antistreptococcus serum prepared under the direction of Dr. Cotton. The reason for this improvement is, I believe, that the resistance of the individual has been enhanced.

As students of intestinal pathology it has been our misfortune that up to the last three years insufficient attention has been paid to the study and eradication of foci in all other parts of the body. The principal locations of these foci are in the tonsils, teeth, abscesses and necroses in the jaw, in the nasal sinuses, rectum, seminal vesicles and cervix uteri. Some of our former patients, who had been improved but not cured by vaccines and general medical therapy or by resection of the right colon, have since been restored to efficiency after the removal of these obvious foci of infection.

These principles are applicable to other diseased conditions, as, for example, in syphilis. Cotton<sup>8</sup> has observed chronic cases that could not be improved until the obvious foci of bacterial infection were removed. This has been my own experience in a limited number of cases. I will cite one case as an example: Male, aged forty years, with tertiary lues untreated for several years, severely affecting the heart, aorta and liver. After four years of the usual antiluetic treatment he improved but still showed a four-plus Wassermann and other signs of luetic activity. This year, after removal of an extensive mouth and jaw infection, with-

<sup>8</sup> Personal Communication.

out further antisyphilitic treatment, the Wassermann dropped to one-plus with other corresponding signs of improvement.

One of the most puzzling aspects of gastrointestinal infection is that it may produce the most profound mental or nervous disturbance, with little or no direct gastrointestinal symptomatology. Attention was called to this by one of our group (Satterlee<sup>9</sup>) in 1917. Careful neurologic study of these patients will reveal no etiologic factor until a detailed and complete study of the gastrointestinal tract and a thorough search for foci in other parts of the body have been made. Eradication of the diseased areas has brought about a return to normal or a great improvement, provided that deterioration has not progressed too far.

In this age of progress a single track is to be avoided and all our faculties must be used in thorough investigation, followed, if justified, by equally thorough treatment.

#### CULTURES FROM APICES OF EXTRACTED TEETH

*Streptococcus mitis* recovered in 37 extracted teeth.

*Streptococcus salivarius* recovered in 24 extracted teeth.

*Streptococcus anginosus* recovered in 7 extracted teeth.

*Streptococcus pyogenes* recovered in 6 extracted teeth.

*Streptococcus equinus* recovered in 4 extracted teeth.

*Streptococcus fecalis* recovered in 3 extracted teeth.

*Staphylococcus albus* recovered in 23 extracted teeth.

*Staphylococcus aureus* recovered in 4 extracted teeth.

Of the streptococci, the *streptococcus anginosus* and *pyogenes* are of the pathogenic hemolytic type, the others—*mitis*, *salivarius*, *fecalis* and *equinus*—are non-hemolytic.

#### CULTURES FROM NECROTIC BONE AREAS

*Streptococcus mitis* recovered in 13 cultures.

*Streptococcus salivarius* recovered in 9 cultures.

*Streptococcus anginosus* recovered in 6 cultures.

*Streptococcus pyogenes* recovered in 3 cultures.

*Streptococcus equinus* recovered in 2 cultures.

*Streptococcus fecalis* recovered in 1 culture.

*Staphylococcus albus* recovered in 8 cultures.

*Staphylococcus aureus* recovered in 1 culture.

No growth recovered in 11 cultures.

Contamination in 1 culture.

It is thus to be noted that in 80 cases in which dental extraction and bone operation were performed the most frequent streptococcic

<sup>9</sup> Jour. Am. Med. Assn., 1917, 69, 1414-1417.

organisms recovered were from the apices and bone, the streptococcus mitis and salivarius of non-hemolytic type. Next the Streptococcus anginosus and pyogenes of the hemolytic type. The Streptococcus subacidus and equi have not as yet been found from our cases.

In analyzing the physical condition of the patients under treatment no conclusions in reference to the type of the organism recovered and the severity of the symptoms can, as yet be drawn.

Where the hemolytic organisms were recovered with one exception, the patients were distinctly ill. In one patient (M. J. C.), where all of the streptococcus organisms except the streptococcus fecalis, subacidus and equinus were recovered, marked cervical adenitis of persistent character was present.

#### CULTURES FROM ANTRA DIRECTLY ON OPENING THROUGH THE MOUTH

Streptococcus mitis, 12	Staphylococcus albus 21
Streptococcus salivarius, 9	Staphylococcus arcus 3
Streptococcus anginosus, 3	Mucosus capsulatus, 1
Streptococcus pyogenes, 5	

These results correspond quite closely to the cultures from the teeth and bone cultures.

CASE I.—A. F., male, aged sixty-one years, retired business man.

*Chief Complaint.* Blood in the urine for twenty years, with occasionally severe hemorrhages. Renal calculus passed at the ages of twenty-four and forty-four, also gravel at times. Nervous depression and inability to work.

*Diagnosis.* Chronic intestinal invalidism with secondary renal involvement.

*Past History.* Scarlet fever twice, at sixteen and twenty-nine years. Slight deafness following otitis media in the right ear. Severe attacks of asthma every summer. Chronic digestive disturbance. Could not carry a light suit-case without a tight abdominal belt.

*Family History.* Brother has had occasional blood in urine.

*Examination.* Enteroptosis, including kidneys, three-plus; nutrition poor. Blood coagulation four minutes. Roentgen-ray demonstrated, no renal calculi. Infected teeth with necrosis and infected antrum. Ureteral catheterization showed red blood cells and occasional leukocytes from both ureters and 18 and 13 per cent of phenolsulphonephthalein in four minutes from the left and right kidneys respectively. Cultures from ureters showed Bacillus communior from both sides. Dental extraction and removal of necrotic areas and drainage of antrum done. Strepto-

coccus mitis and salivarius recovered. Vaccines made from the above colon bacillus isolated by ureteral catheterization administered over a period of six months.

*Results.* Excellent. General condition markedly improved. Patient can play thirty-six holes of golf without fatigue. One slight attack of blood in the urine during vacation when vaccines had been suspended. No attack of asthma this year. Urine examination six months after vaccine treatment began showed no red blood cells and no colon bacilli. Patient has not had so prolonged a period of well-being without hematuria for years.

This case is very suggestive of the connection between oral infection and kidney lesions. It is of speculative interest as to the relationship of the streptococci and the colon bacillus in kidney infections, especially those accompanied by hematuria.

CASE II.—S. F. B., female, aged fifty-four years.

*Symptoms.* Periodic attacks of loss of appetite; "bilious attacks;" "indigestion;" disgust for food and long periods of self-inflicted starvation. Spasm of esophagus on one occasion. Attacks of diarrhea with severe mental depression. Constipation habitual up to two years ago. Medical treatment for hemorrhoids, flatulence and nervous headaches for the past four years. No improvement. Pronounced neurasthenia and hypochondria; irascibility; incoöperative, incompetent, bordering on severe mental derangement. In bed most of the time.

*Examination.* Emaciated, anxious, sallow patient. Extensive fixed bridgework. Numerous capped and crowned teeth. Infected tonsils; hemorrhoids; femoral hernia (reducible). Hemoglobin, 70 per cent, white blood cells, 10,000. Gastric fractional test, 18 per cent subnormal. Mucus 2-plus. Extreme nervous debility.

1. *Dental Operation.* September 26, 1921. Seven teeth removed. All necrotic bone, including floors of both antra, removed. Follicular cysts in the molar areas. Bone necrosis from the roots extended back to the palatal portion of the superior maxilla and to the first bicuspid on the upper right side. In the left antrum there was a catarrhal condition on the nasal side of the antrum opening into the nasal passage. Two openings from the necrosed areas into the nasal passage. Marked improvement.

2. *Tonsillectomy.* Marked improvement.

3. *Hemorrhoidectomy.* Removal of infected crypts. Still more improvement and physical strength greater than in the past three years. Also striking diminution of nervous and mental symptoms. Return of personality to normal.

January, 1922. Bowels regular and practically no digestive disturbance. Enteroantigens (autogenous colon vaccines) caused severe local and constitutional reaction.



This case is one illustrative of marked nervous, mental and physical disorders improved by surgical treatment of certain foci, but not fully relieved until *all* foci had been removed. The improvement in physique and personality has been striking.

CASE III.—A J. LaC., female, aged fifty-two years. Teacher. Hemiparesis; melancholia, suicidal. Progressive constipation for fifteen years. Blood-pressure averaging 235/150. Partial colectomy for diseased ceco-colon and obstructive adhesions in 1914. Marked betterment in mental and physical condition and able to carry on her work. Postoperative condition materially improved by enteroantigens (autogenous colon vaccines). Patient had some dental difficulties with occasional alveolar abscess, but no particular attention was paid to the teeth at the time, 1915-16. Fairly well until 1918, when she had another severe headache with high blood-pressure after extensive dental repair. The phenolsulphonephthalein output on various occasions was well above normal; this with chemical blood examinations demonstrated normal kidney function. In March, 1921, extensive infection in molar regions with necrosis and infected antrum. Operation, with marked general improvement, so that the patient is better today than she has been for over twenty years. Blood-pressure, July 20, 1921, 185/120. This case is typical of the value of the complete removal of all focal infection as early as possible.

---

## INFECTION OF GASTROINTESTINAL TRACT IN RELATION TO SYSTEMIC DISORDERS:

SURGICAL VIEWPOINT: COLECTOMY; INDICATIONS, PATHOLOGY,  
TECHNIC, MORTALITY.\*

BY JOHN W. DRAPER, M.D.

NEW YORK.

FROM the standpoint of infection of the gastrointestinal tract, that portion of greatest interest in surgical research is necessarily the colon. This terminal portion of the bowel is of much less vital need to the organism than the central portion; it is frequently diseased and can be dispensed with, entirely or in part, both in human beings and in the lower vertebrates. The entire problem is thus one of engrossing interest to the specialist and to the general practitioner alike.

\* Read before the New York County Medical Society, at its stated meeting, Academy of Medicine, December 23, 1921.

The similarity between the stomach and the colon has often been noted, particularly as regards their functions, those of storage and motility far outweighing in importance all others. After removal of the stomach in the lower vertebrates, and in man, it has been found that all of its subsidiary functions, as well, apparently, as the two major ones just named, are taken on vicariously by other portions of the tract or indeed largely abrogated. The same is true of the colon. Between the stomach and the colon lies the small bowel, a relatively short portion of which is essential for life. Here, digestion and assimilation take place. Save for the correction of minor conditions, this portion of the alimentary canal is inviolate to surgical intervention, and one has only to initiate the simplest form of surgical research in this region to become convinced that the further invasion of this great laboratory of the body by surgical procedures is improbable.<sup>1 2</sup> In a scholarly paper just published,<sup>3</sup> Eisberg has shown, by what seems to be the most conclusive proof, that the duodenum and the contiguous portion of the jejunum is one of the most highly specialized and least understood portions of the entire body, the beginning and end of the canal decreasing in specialized activity and in obstructive toxicity in a fixed ratio as one departs orally and aborally from the duodenojejunal junction. Why is this so? Why is not the alimentary canal bilaterally symmetrical like all the other great systems of the body? Why finally does the midpart of the canal remain free from disease, notably cancer and infection, while both ends are the frequent seat of malignancy and of bacterial invasion as well?

Is it not probable that the law of use and disuse is as applicable to the alimentary canal as elsewhere in Nature, and that we may properly seek an explanation therein for this well-known clinical fact, that the colon and stomach are more liable to degenerative changes than the rest of the alimentary canal? Closely coupled to this is the now universally admitted effect of gravity upon the development of colon pathology. These biologic and morphologic factors interact and favor at least partial explanations of the surgical findings. Moreover, it cannot be denied that, as Bryant<sup>4</sup> and other students of this matter have shown, men and women are clearly divisible into three definite types, one of which is distinctly unfavorable to the upright position, and from which many cases of chronic intestinal invalidism are recruited. It

<sup>1</sup> Frazier and Peet: Experimental Colonic Stasis, *Ann. Surg.*, June, 1916, **63**, 729-731.

<sup>2</sup> Draper, John W.: Observations upon a Form of Death Resulting from Certain Operations on the Duodenum and Jejunum, *Surg., Gynec. and Obst.*, 1906, **2**, 502-509.

<sup>3</sup> Experimental Intestinal Obstruction, *Ann. Surg.*, 1921, **74**, 584-609.

<sup>4</sup> The Carnivorous and Herbivorous Types in Man, *Boston Med. and Surg. Jour.*, 1916, **174**, 412-416.

is evident that in the course of the adaptations, which were a necessary precedent to the upright position, many changes which would have been beneficial did not take place, and in this matter the colon has proved to be no exception.

In spite of much recently acquired information regarding the colon, notably the fact that even if not diseased its entire removal is compatible with the health, the growth and the development of the individual, its vital functions being apparently *nil*, it cannot be urged too strongly that the indications for its removal, either partial or complete, are rarely to be met with, most cases responding promptly to modern medical treatment. That, however, definite indications for total or partial colectomy are occasionally demonstrable is shown by the increasing literature on this very important subject. One of the most recent articles upon colon resection is that by J. Schoemaker,<sup>5</sup> of The Hague, Holland, who, speaking before the Clinical Congress of Surgeons at Philadelphia, stated that in no less than 179 cases, and with a loss of only 2 patients, he had removed the cecum, ascending colon and part of the transverse colon "in cases with pericolitis associated with obstipation." It is unfortunate that the brevity of this article precludes the further discussion of the indications which led him to the development of this remarkable series.

The subject of colon pathology, particularly in its relation to the etiology of systemic disorders, is at present little understood. This problem is beset with the greatest difficulties from the bacteriologic standpoint, and although much is known about the occurrence of colon lesions in individual cases, enough evidence is not yet available to prove that any particular group of mental symptoms can with certainty be attributed to a given colon pathology. Such evidence is, however, rapidly accumulating. For this very reason the record herewith presented of colon pathology found among 170 toxic psychotic patients at the State Hospital at Trenton is of the utmost importance. For it is only by an accumulation of a large amount of such material, by its careful correlation with all the symptomatology and by a postoperative survey of the patients extending over a number of years, that definite conclusions as to cause and effect can be reached.

Dr. John F. Anderson, who is in charge of the bacteriologic work at the State Hospital, and to whom we are indebted for constructive criticism in the interpretation of our surgical bacteriology, looks upon the problem of colonic infections as still unsolved, but as promising to contribute invaluable information when better understood. Dr. James Ewing's report, herewith appended, upon our specimens supports this position and is convincing, not alone of the extent of the pathology but of the indication for con-

<sup>5</sup> Some Technical Points in Abdominal Surgery, Surg., Gynec. and Obst., 1921, 33, 591-596.

tinued study. Probably we shall have to wait for a further development of the theory of bacterial specificity before being able to obtain from the laboratory a final explanation of these phenomena.

Before considering a partial or total colectomy in any given instance, it is evident, therefore, that the indications—historical, physical and roentgen ray—must be particularly well defined. There must be a long-continued history of chronic intestinal invalidism, with its usual but not invariable evidence of chronic appendicitis early in life, with “bilious attacks” and “bellyaches,” often with oral infections later on, with the occurrence of right-sided abdominal rigidity, and often with tenderness, pain and superficial hyperesthesia, always with colonic delay, defined and localized by roentgen-ray study. Even in the presence of such findings, surgical intervention is, in our opinion, not indicated except there be also well-defined and serious subjective symptoms. It is now eight years since, under the above conditions, our earliest prepsychotic cases were operated upon, and the continued study of these patients not only strengthens our belief in the very important relation of colonic infections to general health, but also affords interesting ground for belief that in many cases there are personality changes associated with chronic intestinal invalidism which may ultimately become fixed in character, constituting definite toxic psychosis. We have reported such changes in childhood and have urged prevention through the recognition and removal of physical causes.<sup>6</sup>

Every practitioner is familiar with the mental depressions which accompany intestinal invalidism, and many must have noted a gradual transition from ordinary depression, apathy and incoordination to well-defined insanity. Often there appears to be a definite gradation between the preinsane and the insane not hitherto recognized, and upon which Cotton's work at Trenton will cast light. Indeed, the establishment of such sequence, or gradation, among the mentally afflicted may prove to be one of the most important results of the development of his theory. Mutation from a simple depression to a definite psychosis certainly occurs with sufficient frequency to interest the general practitioner, and to add to his already great burdens that of early physical diagnosis as an aid to preventive psychiatry. Indeed, prevention is the keynote of the whole matter.

Finally, we feel that no patient should be subjected to colectomy for chronic intestinal toxemia except upon the collective decision of a medical group, it being, in spite of low mortality, a far too serious operation to be decided upon by one physician alone.

In the series herewith presented the evidence for operation based upon ample physical lesions has been augmented by the presence of a psychosis. This has helped to make the decision

<sup>6</sup> Draper, J. W.: Preventive Surgery, New Jersey State Jour. Med., January, 1922, 19, 1-9.

to operate much easier because elective surgical procedures are more properly employed in patients presenting such serious subjective symptoms than otherwise.

The technic at the State Hospital at Trenton for total or partial colectomy is the direct outcome of the writer's experimental work in intestinal obstruction upon the lower vertebrates, so that for technic as well as for interpretation the present research is primarily indebted to the laboratory.<sup>7</sup>

*Technic.* The cecum is lifted mesiad by the assistant and the limiting pericolic membrane is cut with scissors. When this is done the ileocolic vessels are exposed. These are ligated with heavy linen. The right and midcolic vessels are ligated and the bowel is separated from its mesentery. If it has been decided to do a right-sided resection only, the ligation and cutting of the mesentery cease at this point and a heterostaltic lateral anastomosis is made. If the entire colon is to be removed the omentum is split at this point and ligated right and left. This liberates the mesentery and facilitates its ligation. If the splenic flexure is high it will often be necessary to cut across the left rectus muscle, preferably between the tenth and ninth nerves. The flexure should be put on traction mesiad, and the left pericolic membrane and phrenicocolic ligament, which are often fused, carefully separated with scissors points. It is extremely dangerous to make more than the most gentle traction at this point, as the colon is friable at the flexure. The mesentery of the descending colon and sigmoid is then separated as far as the lower sigmoid artery. It is important not to injure this. The patient is then put in the Trendelenburg position and the retroperitoneum is picked up by blunt artery forceps at intervals of about 2 cm. The peritoneum is then tied together, beginning at the bottom of the "U." This obliterates the space into which the bowel would fall between the cut mesentery of the ileum and the sigmoid, and avoids danger of obstruction. The bowel segment is then removed and the anastomosis made heterostaltic and lateral, this having been found to functionate as well as a prostaltic lateral, and end-to-side or an end-to-end anastomosis.

#### MORTALITY OF COLON RESECTIONS AT THE TRENTON STATE HOSPITAL

	Cases.	Deaths.	Per cent.
1919 . . . . .	34	13	40
1920 . . . . .	59	18	30
1921 . . . . .	77	10	12
	(31 complete)		
	<hr/> 170	<hr/> 41	<hr/> 24

<sup>7</sup> Draper, J. W.: Studies in Intestinal Obstruction, Jour. Am. Med. Assn., September 26, 1916, 67, 1080-1082; Intestinal Obstruction, Complete and Incomplete, Jour. Am. Med. Assn., October 7, 1916, 69, 1768-1771.

Decrease due to operating on less degenerated earlier cases in 1920 and in 1921, and in addition to this the employment of anti-eolon and streptoeocus serum before and after operation.

**Conclusions.** 1. Colectomy should never be considered until all other local foci have been removed and the patient thoroughly treated from a modern medical standpoint, especially with vaccines and sera.

2. Extensive eolon pathology exists in 20 per cent of all so-called "functional" psychotics. Mental symptoms have been arrested in 28 per cent of these and improvement has occurred in a large percentage.

3. The mortality of partial (46) and total (31) eolectomy in the past 77 consecutive cases at the State Hospital has been 12 per cent.

**Report on Dr. Draper's Specimens of Colon and Ileum.** BY JAMES EWING, M.D. I have examined sixteen specimens of eolon and ileum removed at operation. The great majority of the specimens show very definite gross anatomic lesions which have resulted from chronic intestinal stasis and the ensuing chronic catarrhal inflammation. In several cases the lesions are extremely marked, in many they are well marked, while in a few there are no definite changes that can be regarded as more than minimal variations from the normal.

The most marked and constant lesion is pigmentation of the mucosa, which has rendered the inner lining brownish or at times dark chocolate in color. This change is most marked in the cecum, diminishing toward the sigmoid, but often present throughout the specimen. Sections show the pigment to be lodged in large polyhedral cells, lying in the mucosa and at times in the epithelium. Pigmentation of the eolon is fully recognized as a sign of chronic intestinal stasis and intoxication. It is sometimes associated with anemia and at times with severe and even fatal dystrophies of nervous and muscular systems.

Pouching of the intestinal wall amounting almost to hernial protrusions was observed in most of the cases. These pouches were from 1 to 2 cm. in depth. The wall of the pouches was generally thinned, sometimes very much thinned, and the mucosa at the bottom was generally eroded, sometimes ulcerated. Through such erosions and ulcerations it is obvious that absorption of fluids and bacteria readily occurred. The usual contents of these pouches must have been fecal matter, and it appears that such material must have been practically incarcerated and seldom emptied. About the lower end of the cecum the pouches were especially numerous and deep, and access to them was tortuous, especially when external adhesions held the wall of the eolon fixed.

The outer surface of the eolon over the pigmented, and especially over the pouched district, was generally the seat of a chronic productive inflammation with the formation of very numerous

small granules of vascular connective or denser fibrous tissue. This granular appearance was doubtless exaggerated by hardening in formalin.

The loose serous coverings of the colon generally appear as thin membranes extending from the gut over the mesentery. These coverings often showed diffuse opacity from thickening, abnormal bands and striæ, and occasionally definite cicatricial contractions. To what extent these changes were due to the conditions inside the gut it is difficult to say, but probably they were largely caused by the mucous membrane lesions.

The lymph nodes in the mesentery accompanying the specimens were not, as a rule, enlarged, and often they were small and difficult to find. Sections of the nodes showed no inflammatory reaction of definite importance. It was noted that the lymph follicles were generally invisible in the colon and were reduced to a trace in the sections. Well-formed, recognizable Peyer's patches were not found in any case. There was therefore a general atrophy of the lymphoid apparatus inside and outside of the gut. That bacteria were found by culture in the lymph nodes of the mesentery could have been confidently predicted on the lesions of the mucosa and the lymphoid atrophy.

In general the impression gained from the study of these specimens was that the clinicians were dealing with extensive and somewhat unusual grades of chronic intestinal stasis and catarrhal inflammation with its sequels. In a few cases the conditions were such as to be practically irremediable except by mechanical straightening of the intestinal lumen. Whether or not extirpation of the cæcum is the most direct method of accomplishing this object must be a matter of surgical judgment.

In perhaps the majority of the cases, and certainly in some, the conditions were not so advanced that emptying of the colon was impossible by lavage or frequent catharsis. Here, again the choice of methods must be regarded as a matter of clinical judgment. As for the specimens of ileum submitted, they failed to show any lesions that would necessarily call for extirpation. The indications for this procedure must rest entirely on clinical grounds.

The isolation of various bacteria from the mesenteric lymph nodes does not appear to have particular significance, since bacteria pass the relatively intact intestinal wall under a great variety of pathologic conditions, many of which have no connection with the clinical state of these patients. More important is the demonstration of hernias, pouching, thinning of wall, pigmentation and ulceration of the mucosa, which together form an impressive anatomic basis for the theory of intestinal intoxication, which undoubtedly existed in severe degree in the cases exhibiting such lesions.

Finally, I would venture to express my personal opinion that extirpation of the affected portions of the cecum and colon was justifiable and probably the only effective means of relieving the condition found in the advanced cases, while in others with slight changes the condition could have been met by less radical means. The extirpation of considerable portions of the ileum appears to me unwarranted if based solely on the anatomic condition of this organ.

---

## INFECTION OF THE GASTROINTESTINAL TRACT IN RELATION TO SYSTEMIC DISORDERS.

### NEUROLOGICAL VIEWPOINT; SPECIAL RELATION OF CLINICAL SYMPTOMS TO REGIONAL DISTRIBUTION OF FOCAL INFECTION.

BY HENRY A. COTTON, M.D.

TRENTON, N. J.

IN presenting a psychiatrist's viewpoint of the relation of focal infections to systemic disorders before an audience of general practitioners, one must at the outset disabuse the mind of the physician of the timeworn traditional theories regarding the psychoses. Heretofore cases suffering from mental disorders were viewed with alarm by the general practitioner, through no fault of his own, however. The psychoses were elevated to a plane far beyond the vision of the physician. The symptoms were not understood and he felt helpless. The natural outcome of this situation was that psychotic patients were immediately committed to an institution for the insane.

This situation arose largely from our previous lack of knowledge of the causes of the various psychoses, and consequently there was no adequate treatment which could be instituted in the early stages of the mental disorder. Our fundamental knowledge of the psychoses has been based largely on speculation and coincidence, and the causes of the mental disorders were rather obscure and therefore no specific treatment could be instituted.

One of the most prevalent errors as to the causation is that of heredity. So fixed has this become in the minds of the profession and laity, and I might add psychiatrists as well, that it has been considered the principal, if not the fundamental, cause of the psychoses. This fact arose from the rather loose way in which records of heredity were gathered in the old state hospital statistics. Any patient in which there was "insanity in the family" was



noted as suffering from a hereditary taint. This occurred in sufficient numbers to substantiate the opinion that the psychoses were hereditary in origin.

It is needless to go into the various arguments from a biologic standpoint to show that this theory is erroneous. Not only were we in serious error regarding heredity, but such a doctrine was extremely fatalistic. For if a patient was born with the potential elements of mental disorder, then there was little use in trying to prevent the psychosis or to successfully arrest it if it had appeared. Hence, the attitude was adopted that only by methods of training, education and favorable environment could these symptoms be forestalled. But we have seen many cases in which the environment was extremely favorable to the individual, where education and training were all that could be desired, and, in spite of this, psychoses developed.

In spite of the fact that perhaps 70 per cent of our patients give a history of "insanity in the family," especially in the institutional types, largely of the indigent class, there still remains a large percentage in which no hereditary taint can be discovered. The result of some five years' intensive study of the hereditary factors in the psychoses led the writer to a certain degree of skepticism regarding the importance of this factor, and today, while we do not eliminate the influence of an hereditary taint and its consequent inherited predisposition entirely, at the same time we are of the opinion that heredity should not occupy the exalted position it has previously held. As it has no bearing on the prognosis of a given case we believe that discussion is at present merely academic.

**Psychogenic Factors.** For many years the psychiatrists, in common with the profession at large, voiced the opinion that the psychoses were purely mental disorders caused by hereditary instability, plus psychogenic or mental factors. The physical condition of the patient was absolutely neglected, and our attention was centered alone on the psychogenic factors and the mental symptoms. This gave rise to a fundamental error in that we assumed the psychoses to be diseases of the mind caused by mental factors almost exclusively.

As no demonstrable lesions had been found in the brain cortex, it was considered that these disorders were "purely functional"—in other words that the disease of the mind was independent of any pathologic changes in the brain tissue. With an improvement in the methods of studying brain tissue and the results of our work the last four years, we have slowly arrived at the conclusion that the so-called functional psychoses were in reality caused primarily by disease of the brain and not of the mind, and that the mental disorders were merely symptoms of a diseased brain. The writer, working under Alzheimer in 1905-1906, produced conclusive evidence that there were changes in the nerve cells of

the so-called functional disorders, and this laid the groundwork for the future development of the idea that we must look to the anatomic lesions in the brain if we were to successfully arrest the psychoses, and, which is still more important, prevent them in time.

We would emphasize the fact that we do not minimize the importance of the psychogenic factors in precipitating a psychosis as we see a certain proportion of our cases in which such psychogenic factors as grief, worry, anxiety, shock and a host of others are present and undoubtedly play an important role in precipitating the psychosis. However, we have observed many cases in which these psychogenic factors are entirely absent. Hence, we have been forced to conclude that these factors, as in the case of heredity, play an important, but not the most important role, in the causation of the psychoses of the "functional" types.

**Infection.** If then we have destroyed our belief in the important role of heredity and psychogenic factors, what have we to offer in their place as causative factors? Formerly the physical condition of the patient was of minor consideration and many patients were classed as physically normal, which practice we know now was a serious error. We are indebted to modern mental practice for the methods which permit the finding of serious physical disease in apparently otherwise healthy individuals. The work of Billings, Hastings, Rosenow, Barker and Upson of the medical as well as Thoma and others of the dental profession has established, without any question of doubt, the doctrine of focal or masked infections. These infections were formerly overlooked not only in the psychotic patient but in patients suffering from various systemic disorders. This doctrine has been the most important contribution of twentieth century medicine and the application of the methods evolved to determine the presence of chronic infection has added an entirely new chapter to the treatment and prevention of the psychoses.

That local foci of infection which give no local symptoms and of which the patient may be ignorant can cause serious systemic diseases, both by spread of the organisms to other parts of the body and by a dissemination through the blood streams of the toxic products, the result of such infection, is still doubted by many; but we feel that enough work has been done to establish such a doctrine in spite of this skepticism.

Our investigations in the last four years have shown conclusively that the psychotic individual harbors multiple foci of infection which often can be located and eliminated only with the greatest difficulty and persistence on the part of the physician. In order to properly locate and eliminate these multiple foci of infection the psychiatrist has had to call to his assistance the specialist in other branches of medicine. So that today a well-equipped clinic for nervous and mental disorders is only adequate in so far as this principle of group diagnosis is carried out. The growth

of the idea of a diagnostic survey of every individual, whether suffering from mental disorder or other systemic diseases, has been rapid. One need only to mention the success of the Mayo Clinic and of the work of Lewellys Barker at Johns Hopkins to illustrate the trend of modern medicine. Why then should there be any criticism if the psychotic individual is given the advantage of the application of the principles of modern progressive medicine? In view of the successful application of these principles at the State Hospital at Trenton in the last four years, shall we still adhere to the old ideas expressed at the beginning of this paper, or shall we lay prejudice aside which limited the treatment of the psychoses to psychotherapy or the so-called occupational therapy and study the individual as a whole and endeavor to discover any pathologic condition which might be present?

It is only within the writer's short experience of twenty-one years that the question of the relation of syphilis to paresis was doubted in America. Paresis was considered a disease due to overwork, or mental strain, because it occurred in brokers, bankers, actors, and others who were supposed to be overworked. It was considered purely a mental disease. First a history of previous syphilis in a large proportion of the cases gave a clue to a better understanding of the causation. Then the studies of the brain cortex by Nissl and Alzheimer revealed the fact that very serious pathologic changes had occurred. Finally Moore and Noguetli demonstrated the *Spirocheta pallida* in the brain tissue in cases dying of paresis. Here we have an example where, step by step, our ideas regarding the causation of paresis underwent a complete revolution and no one would dispute the fact today that paresis is an organic brain disease due to destruction of the brain tissue by the *Spirocheta pallida*.

The so-called functional psychoses we believe today to be due to a combination of many factors, but the most constant one is the intracerebral, biochemical and cellular disturbance arising from circulatory toxins originating in chronic foci of infection situated anywhere throughout the body and probably secondary disturbances of the endocrine system. The psychoses then, instead of being considered a disease entity, should be considered as a *symptom*, and often a *terminal symptom*, of a long-continued masked infection, the toxemia of which acts directly on the brain. As psychiatrists have for years recognized a toxic infectious psychosis, especially in patients who had an obvious infection, acute in character and easily diagnosed, we have not established a new principle when we speak of the toxic origin of some psychoses. But we have extended the diagnosis to include types such as manic-depressive insanity, dementia precox, paranoid condition, etc., in which the infection is not apparent or easily found upon causal

examination. But such infection is only found upon utilizing all the methods of modern diagnosis, so it should not be difficult to adjust our ideas to these views.

If the profession at large can accept this viewpoint, which we feel we have demonstrated beyond a reasonable doubt, then their attitude will be changed from a hopeless, fatalistic one, previously in vogue, to a hopeful one wherein they themselves cannot only arrest many cases after a psychosis has developed, but, better still, by eliminating these foci of infection easily prevent the occurrence of the psychosis. There can be no question that many of the psychoses can and will be prevented when the result of such infection is properly understood by the profession at large. It is obvious that when the psychoses can be arrested by eliminating chronic foci of infection, then by properly treating such patients long before the psychosis appears the mental disorder can be prevented.

**Source of Infection.** We have found that the source and type of chronic infection in the psychotic patient is the same as found in many of the systemic disorders. We may be pardoned, perhaps, if we claim that our work in the elimination of focal infection has gone further than in most clinics. We have utilized what we consider the best methods that have been developed. Some of them, unfortunately, are not in general use, nevertheless we are of the opinion that time will show that all the methods adopted by us are extremely valuable in ridding the patient of multiple foci of infection until better methods are devised.

We have come to regard the infection of the teeth as the most constant focus found in our patients. Without exception the functional psychotic patients all have infected teeth. Briefly they may be divided into unerupted and impacted teeth, especially the third molars; periapical granuloma; carious teeth with infection; apparently healthy teeth with periodontitis; devitalized teeth with either Richmond or gold shell crowns; extensively filled teeth with evidence of infection; and gingival granuloma in apparently vital teeth.

While the progressive men and leaders of the dental profession are awake to all these types of infection, unfortunately the "rank and file" are not sufficiently acquainted with these many forms. Consequently the physician who attempts to rid his patient of focal infection must become acquainted with modern dental pathology. In our younger patients, from sixteen to thirty years of age, no matter what the psychosis may be diagnosed, we find unerupted and impacted third molars in a large proportion of the cases. And we would unhesitatingly advise, when there are clinical evidences of systemic infection and intoxication present, that these should be removed. We have found that they are always infected, and the infection is in some way related to the

fact that the tooth is unerupted and impacted. All crowns and fixed bridgework have been condemned by the best men in the dental profession, and we voice the same opinion. So in order to rid a patient of focal infection a very thorough job must be done and no suspicious teeth allowed to remain. This does not mean that every patient should have all his or her teeth extracted. In fact, in our work at the State Hospital we would not average over five extractions per patient.

Time prevents my going into the question of infected teeth more thoroughly, but I would emphasize the fact that a thorough elimination of focal infection can only be obtained by extraction. All other methods have proven worthless and dangerous to the general health of the individual.

We should like to call attention to the method of removing the infected teeth. In many cases simple extraction is not sufficient even when the socket is thoroughly curetted. When the alveolar process is severely involved the Novisky method of surgical removal is absolutely necessary. Failures to get results from removing infected teeth are frequently due to the fact that diseased, infected, necrotic bone is left and absorption continues even after the teeth are extracted.

Chronic infection of the tonsils is equally important as infected teeth, and the mouth cannot be considered free from infection when infected tonsils are not removed. It is a striking fact that very rarely is a patient admitted to the State Hospital at Trenton whose tonsils have been previously removed, so that over 90 per cent of the patients have to have their tonsils enucleated after admission. That the children of the present generation are having their infected tonsils enucleated will, we believe, have a definite influence on the elimination of systemic and mental disorders later in life. Whatever may be the result of treating infected tonsils with the roentgen ray or local therapy, we feel that today enucleation is the only method permissible.

**Types of Bacteria Concerned in Chronic Infection.** Briefly stated, we have found the various types of streptococci and colon bacilli responsible for chronic infection in our psychotic patients. The streptococcus group composes many strains, as cited below. The colon bacillus group is also made of various strains, differentiated by their cultural reactions in carbohydrate media.

Below is given a table showing the strains of streptococci classified according to Holman. These sixteen types represent the grouping of 1122 strains of Holman, and taken with strains from the literature, the total number is 2463, a sufficient number to come to some conclusion as to their biologic types. While some types can be identified under the microscope, only by their cultural reactions can they be accurately differentiated.

## HEMOLYTIC STREPTOCOCCI

Type.	Mannite.	Lactose.	Salicin.
Infrequent . . . . .	Plus	Plus	Plus.
Hemolytic, i . . . . .	Plus	Plus	Minus.
Pyogenes . . . . .	Minus	Plus	Plus.
Anginosus . . . . .	Minus	Plus	Minus.
Hemolytic, ii . . . . .	Plus	Minus	Plus.
Hemolytic, iii . . . . .	Plus	Minus	Minus.
Equi . . . . .	Minus	Minus	Plus.
Subacidus . . . . .	Minus	Minus	Minus.

## NON-HEMOLYTIC STREPTOCOCCI

Fecalis . . . . .	Plus	Plus	Plus.
Non-hemolytic, i . . . . .	Plus	Plus	Minus.
Mitis . . . . .	Minus	Plus	Plus.
Salivarius . . . . .	Minus	Plus	Minus.
Non-hemolytic, ii . . . . .	Plus	Minus	Plus.
Non-hemolytic, iii . . . . .	Plus	Minus	Minus.
Equinus . . . . .	Minus	Minus	Plus.
Ignavus . . . . .	Minus	Minus	Minus.

We have so far been able to isolate six strains of the hemolytic group, *i. e.*, the infrequent, pyogenes, anginosus, equi and subacidus, and five strains from the non-hemolytic group, *i. e.*, fecalis, mitis, salivarius, equinus and ignavus. We have found representatives of both these groups in various sources of culture. Occasionally the hemolytic strains are found in the teeth, but more frequently this type is found in the tonsils and gastrointestinal tract. Nine-tenths of the tonsils harbor the hemolytic strains, and often the non-hemolytic strains as well, and it is not unusual to find two or three strains in the culture from the stomach and duodenum, both hemolytic and non-hemolytic types.

Later investigations have shown the "viridans" is a form of the non-hemolytic streptococcus, but not all of the latter can be classed as "viridans." So it is better to substitute the exact type for this term.

It is useless to argue which types may or may not be pathogenic, or which types may be more virulent than others. We have not found that the hemolytic types were more virulent than the other group or that they produced more marked symptoms. In fact, any of these organisms may become so virulent at any time that they cause the death of the patient, although for a long time they may be latent and no marked evidence of their presence shown other than by the fixation tests. We are still of the opinion that the complement-fixation tests of the blood for determining the presence of chronic infections are of value, as are also the agglutination tests for the same purpose. Further standardization is necessary, however, before they can be used as a routine laboratory test.

**Dissemination of Infection.** From the fact that the elimination of infected teeth and tonsils produced marvellous results in some cases and in others no results whatever, it was logical to conclude that the infection had spread to other parts of the body, through either the lymphatic circulation or the blood stream, and preferably by the former. Secondary infection of the stomach and lower intestinal tract could also come from constantly swallowing the bacteria originating in the mouth, so that we find secondary foci of infection of the stomach, duodenum, small intestine, gall-bladder, appendix and colon. The genito-urinary tract is frequently infected not only by the organism of the streptococic group but by the colon bacillus group as well. The source of this infection of the genito-urinary tract is not altogether known.

In the females we find at least 80 per cent of the cases have a chronic infection of the cervix uteri, and while the body of the uterus is rarely involved, we more frequently find infection in the adnexia. In the males a certain percentage of the acute psychoses have infection of the seminal vesicles. The prostate and bladder, as a rule, are not involved.

**Treatment by Detoxication.** It should be evident from what has been said that all surgical measures utilized are primarily for the elimination of the chronically infected tissue. It has no relation to the surgery practised some years ago which was directed toward correcting malpositions and the removal of ovaries and other organs irrespective of infection.

The removal of all infected teeth and infected tonsils is imperative. Surgical measures have been utilized for removing portions or all of the infected colon. The Sturmdorff method of enucleating an infected cervix has proved very successful. When the uterus and adnexa are involved a complete hysterectomy is necessary, and involvement of the seminal vesicles necessitates excision and drainage:

Chronic gastric infection and infection of the small intestinal tract can only be treated by autogenous vaccines or specific serum. Autogenous vaccines are made in our laboratory from the bacteria isolated from the stomach by the Rehfuss method. We have also developed a specific antistreptococci and anticolon bacilli serum made from the organisms isolated in our laboratory. Every patient receives as routine treatment, first, the autogenous vaccine and later the specific serum. But always after infected teeth and tonsils have been removed. The serum has proved especially valuable in the operative cases. Its administration before operation upon the colon has reduced the mortality from 30 to 12 per cent. Therefore if for no other reason its use is justified.

I shall leave to others a detailed discussion of the gastrointestinal infection and the infection of the genito-urinary tract.

**Results of the Work.** We have outlined above our theories regarding the causation of the so-called functional psychoses. We realize that many theories have been advanced in the last fifty years regarding this subject, but we also want to state that during this time the recovery rate of state institutions has materially diminished. If then we advanced merely a new theory and could not show that the application of such a theory had had unusual results on our patients, we should then be classed with the theorists and our work considered interesting if true. However, we feel that we have substantial grounds for considering that the application of these theories has produced results which, as Meyer states, "Appear to have brought out palpable results not attained by any previous or contemporary attack on the grave problem of mental disorder."

We will confine our statistics to the so-called functional group, which includes dementia precox, manic-depressive insanity, paranoid conditions and the psychoneuroses. In this group, as a whole, for a ten-year period prior to 1918 the recovery rate was only 37 per cent of the admissions. Since 1918 the recovery rate has averaged nearly 70 per cent in the same group. Of 380 cases classified in this group in 1918 only 50 today remain in the hospital, and 9 of these are criminals. A recent survey made of these 380 patients discharged in 1918 shows that after three years, with few exceptions, they are today normal in every respect. Over 1000 patients have been successfully treated in the last three years, and it is gratifying to note that the proportion of readmissions to the State Hospital at Trenton has not increased during this time, and that many of the readmissions are cases that were admitted, the first time, prior to this period of intensive treatment.<sup>1</sup>

Our failures have been confined to the patients with a psychosis of over two years' duration. The cause for such failures we consider is due to the fact that the brain has become permanently damaged and no amount of elimination of such infection has any effect upon the psychosis.

**Conclusions.** We have produced evidence, both clinical and pathologic, which should set at rest any doubt as to the accuracy of our deductions. The fact that many individuals harbor focal infections and are not insane is no argument against the doctrine that focal infections can cause insanity. We know that only a small proportion of patients contracting syphilis develop paresis. In the same way we know that only a small proportion of those indulging in alcohol excessively develop a psychosis. Some individuals are able to drink a great deal without showing any symptoms, and in other individuals it takes only a small amount to produce a psychosis.

<sup>1</sup> On July 1, 1922, the successfully treated cases numbered 1400, and only 50 (or 3 per cent) have returned and are still in the hospital.



One may argue similarly regarding a functional psychosis. The type, specificity and severity of the infection, plus the patient's constitutional lack of resistance, determine whether or not a psychosis will develop. Such factors as heredity and psychogeneses undoubtedly play an important role; more, however, we now think, as precipitating the psychosis rather than as causing it.

---

## THE APPLICATION TO OTHER INSTITUTIONS OF THE RESULTS OF TREATMENT OF THE INSANE IN TRENTON STATE HOSPITAL.

BY BURDETTE G. LEWIS,

STATE COMMISSIONER OF INSTITUTIONS AND AGENCIES OF NEW JERSEY.

It is naturally very gratifying to me to note the success in New Jersey of work which I undertook in New York, but which for want of time I was never able to carry through to completion. While Commissioner of Correction in the City of New York, I undertook to transplant to the old correctional institutions of the city and to the two new reformatories many of the routines and practices of the best hospitals for the insane. We discovered that many men and women in prison or in the reformatory were either insane or unstable, or were epileptics or feeble-minded, or were not able properly to conduct themselves as normal beings. We also discovered that the disciplinary difficulties of correctional institutions were almost entirely due to the presence of persons belonging to these various groups who had been sentenced to prison or to a reformatory. By inquiry among the best hospitals for the insane and the best institutions for the treatment of the unstable, the epileptic and the feeble-minded, we found that the disciplinary difficulties of such institutions had been solved not by the club and the gun and by invoking horrible imprecations and profanity, but by the intelligent application of modern therapy and modern treatment, with which physicians have now become quite familiar.

The organization of the New Jersey Department is such that work which was difficult in New York, where the departments were under separate jurisdiction, is very simple in New Jersey, where all of the institutions are in a single department. This has made the transplantation of the best practices of the particular institution to all the other institutions a much simpler problem. Take, for example, mental and medical work in the correctional institutions. Here we organized a psychiatric clinic and placed the doctors and the psychologists under the general supervision of Dr. Cotton, who holds the position not only of Medical Director

of the State Hospital at Trenton but also of Acting Director of the Division of Medicine and Psychiatry of the Central Department. This plan has hastened the application of the best tested results of the State Hospital to all the correctional institutions. Cases are discovered in the correctional institutions which are in need of treatment at the hospital, and under our law they are transferred to the psychopathic division of the hospital long before they have become insane from the legal viewpoint.

The influence of the psychiatric clinic upon medical work of the institutions has been very great. The treatment of the mouth, the removal of tonsils, the clearing up of gastrointestinal infection, the development of surgical procedures and the all-around treatment of the individual which is carried out at the Trenton Hospital have shown the desirability of extending the benefits of such medical, surgical, and other treatment to all of the population of each correctional institution. In consequence the medical service and the appropriations for medical service have been more than trebled in all the institutions. The expense of this has been reduced by reason of the fact that the psychiatric clinic cuts down the cost of overhead supervision of physicians and by reason of the fact that the increase in the amount of medical work in each institution has stimulated coöperation with the physicians of the various communities in which the various institutions are situated. The amount of voluntary work performed by physicians in connection with our institutions has been more than quadrupled in the last three years. It is obvious, therefore, that we are deeply indebted to the physicians in regular practice throughout the state for many of our good results. We found, for example, at the State Home for Boys, an institution for juvenile offenders, that at least 65 per cent of the boys were in need of minor operations; that only 3 per cent of them had the benefit of such operations before reaching the institution. A group of twenty physicians has volunteered to help in the work which has been going forward in that institution for more than a year. We have also changed the personnel and improved the scholastic and other work which is carried on for these boys. The results speak for themselves. Three and a half years ago one out of each two boys released from that institution upon parole failed, now only one out of each ten fails.

The development of research work at Trenton has stimulated similar work in other institutions, and has won for us legislative appropriations for treatment instead of mere custody of patients. Morris Plains State Hospital, for example, has under the course of construction a 400-bed treatment hospital, which will permit the carrying out of the very best types of medical treatment at that institution. Our plans call for the provision of additional buildings at the Morris Plains Hospital and at the Trenton Hospital,

so that each institution will in fact be two institutions, one for the medical treatment of new cases and of the cases which have been in the institution for only a short time, and the other institution for the chronic cases which are beyond reasonable hope of recovery.

We are attempting to extend to the people of our various communities the results of these achievements in the institutions through the establishment of clinics. There is not time to go into details, but suffice it to say that the physicians in our state institutions are to secure the advantage of handling the new cases in the communities long before they would ever reach a state hospital. On the other hand, the patients in the state institutions are to reap the benefit of the enthusiasm of doctors whose efforts are stimulated by contact with mental disease in the earlier stages of its development; for you physicians, I am sure, fully realize how, perhaps unconsciously, hospital physicians fall into the rut and feel that there is little use of extensive work upon cases which have become chronic in so many instances before they reach the state hospital.

We are deeply indebted to men like Dr. John W. Draper, who has so freely given up his time and his expert abilities in the promotion of our work, at no small sacrifice of time and strength. New Jersey is indeed fortunate in securing their help, and is proud of the results achieved.

---

## CARCINOMA OF THE ESOPHAGUS WITH PERFORATION OF THE AORTA: OBSERVATIONS ON RADIUM THERAPY.

BY JAMES G. CARR, M.D.,

AND

C. W. HANFORD, M.D.,

CHICAGO.

PERFORATION of the aorta complicating carcinoma of the esophagus is of infrequent occurrence. There is a curious similarity in most of the statistical reports regarding the relative frequency of such perforations. Hampeln<sup>1</sup> found 2 cases of perforation in the aorta in 57 autopsies on subjects dead of esophageal carcinoma. Mampell<sup>2</sup> saw two such perforations in a series of 50 autopsies. Taylor<sup>3</sup> quotes Ewald thus: "In 40 to 50 cases of carcinoma of the esophagus I have only known 1 to perforate the aorta." Knöpfler<sup>4</sup> refers to Eichhorst's series in which perforation of the aorta was found once in 34 cases, and also quotes Petri's statistics of 44 cases, with 1 instance of aortic perforation and 2 of perforations of intercostal arteries. Very different figures were given by

<sup>1</sup> St. Petersburg med. Wehnschr., 1903, 20, 423.

<sup>2</sup> Inaug. Diss., Ueber den Speisenrohrkrebs, 1904.

<sup>3</sup> Lancet, 1896, 1, 991.

<sup>4</sup> Inaug. Diss., Zur Casuistik des Ösophagus Carcinoms, 1900.

v. Ziemssen and v. Zenker as quoted by Hess<sup>5</sup> and Knöpfler.<sup>4</sup> This analysis of 116 cases included 18 of perforation of the aorta.

In 1896 Knaut<sup>6</sup> collected all the reported cases of perforation of the aorta as a complication of carcinoma of the esophagus. The first case he found was reported by van Doeveren in 1789. Knaut's review of the cases in the literature included perforations of other large vessels. He believed such perforations to be very rare and quoted Leichtenstern to this effect: "Perforations of the aorta and vena cava are most rare." Taylor collected 8 cases in 1889 and in 1895 Vierhuff<sup>7</sup> cited 8 cases with this remark: "The cited 8 cases of perforation of an esophageal carcinoma into the aorta are the only ones found in the literature." Neither Taylor nor Vierhuff could have known of the statistics of v. Ziemssen and v. Zenker.

Knaut's series included 50 cases. Among these there were 32 of perforation of the thoracic aorta and 2 of the aortic arch. Twice the left common carotid was perforated; twice the left subclavian. The left internal carotid, the right subclavian and the esophageal artery were each perforated once. In 1 case the first, second and fourth intercostal arteries were involved; in another the esophageal vein was perforated; while the portal vein was opened once by a growth originating in the lower part of the esophagus. In 2 cases mention was made of "aortic branches" as the source of the terminal hemorrhages without further details, while the source of the hemorrhage was undetermined in 1 other case; here there remained a question as to whether the left common carotid artery or the left jugular vein was ruptured.

The series included 3 cases in which no actual perforation had occurred. In 2 of these the wall of the left auricle showed carcinomatous invasion; in 1 of these cases a cerebral embolus was the cause of death; in the other the statement was made that there were cerebral symptoms late in the course of the disease. In the third case there was a thrombus beginning in the right azygos vein, extending into the superior vena cava and thence to the right auricle.

Since Knaut's publication we have found 21 cases in the literature, including, as Knaut did, perforations of the aorta and large vessels. The first case reported subsequent to Knaut's paper was that of Taylor;<sup>8</sup> there was a perforation of the descending aorta about two and one-fourth inches below its commencement. Drozdowski,<sup>9</sup> Garrod<sup>10</sup> and Mader<sup>11</sup> each reported cases of "per-

<sup>5</sup> Inaug. Diss., Ueber Perforationen bei Oesophagusearcinom, 1902.

<sup>6</sup> Inaug. Diss., Berlin, 1896.

<sup>7</sup> St. Petersburg med. Wehnschr., 1896, N. F., 13, 195.

<sup>8</sup> Loc. cit.

<sup>9</sup> Russk. Arch. patol. klin. Med. u. Bakteriolog., 1896, 1, 557 (quoted by title).

<sup>10</sup> Tr. Path. Soc., London, 1897-8, 49, 92.

<sup>11</sup> Jahrb. Wiën. K. K. Krankenanstalten, 1897, 6, Pt. 2-207.

foration of the aorta." Moore's<sup>12</sup> case was diagnosed clinically as aneurysm: "The absence of anything resembling cancerous cachexia or of any constitutional disturbance and the presence of a whole group of pressure symptoms led me to the belief that the lesion was most likely an aneurysm." Sudden death followed a profuse hemorrhage; at autopsy there was found a perforation of the right subclavian artery. Finley and Anderson<sup>13</sup> reported a case of perforation of the left subclavian artery. Yepifanoff's<sup>14</sup> case was one of perforation of the right common carotid. In Mauclaire's<sup>15</sup> case a perforation of the transverse portion of the aortic arch occurred some six months after a successful gastrotomy. Knöpfler's<sup>16</sup> case was one of perforation of the aorta about the level of the bifurcation of the trachea. Minnich<sup>17</sup> merely reported a case of perforation of the aorta without further specifications. The case of Biggs<sup>18</sup> was like that of Mauclaire; three months after a successful gastrotomy the perforation occurred. The cases of Hollos<sup>19</sup> and of Hart<sup>20</sup> were perforations of aortic aneurysms. Hampeln<sup>21</sup> reviewed his autopsy records of 57 cases of esophageal carcinoma; the series included 2 cases of perforation of the aorta; anatomic details were not discussed. In Davidsohn's<sup>22</sup> case there was a very small communication between the aorta and the esophagus; the stomach contained a quart or more of blood. Mampell<sup>23</sup> analyzed the autopsy records of 50 cases of esophageal carcinoma; perforation of the aorta was recorded once; there was a further record of perforation of an intercostal artery. In Guy's Hospital Reports<sup>24</sup> for 1905 there is a record headed: "The aorta opened by an epithelioma of the esophagus." Deve's<sup>25</sup> case was one of latent carcinoma of the esophagus, which terminated very suddenly; at autopsy a perforation of the thoracic aorta was found. Levy, Yalenski and Godlewski<sup>26</sup> reported another latent case, "Clinically without symptoms of esophageal disease" a "foudroyante" hemorrhage occurred; autopsy disclosed a rupture of the aorta in association with ulcerating carcinoma of the esophagus. In addition to these cases of actual perforation Hess<sup>27</sup> described an extension of the carcinomatous process to the wall of the left auricle; "The wall is permeated by firm, whitish tumor masses, which are connected with the tumor masses originating in the esophagus."

<sup>12</sup> Dublin Jour. Med. Sci., 1898, 105, 396.

<sup>13</sup> Montreal Med. Jour., 1899, 28, 125.

<sup>14</sup> Bolnitsch. gaz. Botkina, St. Petersburg, 1901, 12, 522 (quoted by title).

<sup>15</sup> Bull. et mém. Soc. anat. de Paris, 1901, 6 S, 3, 256.

<sup>16</sup> Loc. cit.

<sup>17</sup> Pest. méd. chir. Presse, 1902, 38, 941. (quoted by title).

<sup>18</sup> Proc. New York Path. Soc., 1903-4, 3, 1.

<sup>19</sup> Pest. Med. Chir. Presse, 1903, 39, 357 (quoted by title).

<sup>20</sup> Zeitsch. f. Krebsforschung, 1905, 3, 278.

<sup>21</sup> Loc. cit.

<sup>22</sup> Deutsch. med. Wehnschr., 1904, 30, 409.

<sup>23</sup> Loc. cit.

<sup>24</sup> Guy's Hosp. Reports, London, 1905, 19, 396.

<sup>25</sup> Revue méd. de Normandie, 1907, 8, 95.

<sup>26</sup> Bull. et mém. de Soc. anat. de Paris, 1910, 35, 140.

<sup>27</sup> Loc. cit.

Vierhuff<sup>28</sup> and Hart<sup>29</sup> discussed the pathogenesis of such perforations. Vierhuff expressed the opinion that the wall must be diseased before the perforation occurs; "The wall of the aorta must undergo carcinomatous degeneration to supply the conditions for perforation." Hart saw "the occasion for the perforation in the advance of gangrenous destructive processes." Opinions such as these have found general acceptance.

The case which we report was seen at the County Hospital on the service of Dr. Joseph A. Capps, through whose courtesy the records have been placed at our disposal.

S. S., aged forty-five years, male, in preprohibition days a bartender by occupation, was admitted to the hospital on June 3, 1920. He complained of loss of weight, pain in the chest, difficulty in swallowing and regurgitation of food. The difficulty in swallowing had been present for three months; at first only solid foods, especially large particles of the same, caused the dysphagia, but the condition was aggravated until upon admission it was possible for him to swallow only liquid or soft foods; the act of swallowing such foods was associated with sharp, shooting pain in the chest. There was some thoracic pain most of the time. This pain was localized particularly about the midsternal region. Unless the food was taken very slowly regurgitation occurred. Aside from a history of alcoholism, including an attack of delirium tremens sixteen years previously, his personal and family history was negative. Physical examination was generally negative. The Wassermann reaction was negative. Roentgen-ray examination on June 4, disclosed: "A partial obstruction in the middle third of the esophagus. This narrowing is irregular in character and indicates an extensive lesion, probably malignant."

Beginning June 21, radium therapy was employed with fluoroscopic control; "The end of the metal container is seen to lie in the substance of the growth as evidenced by the barium shadow at the site of the lesion." Further treatment was given on June 22 and 24 and on July 26. On August 24 examination (roentgenologic) showed "considerable deformity of the esophageal walls, although very much less so than on previous examinations." There had been distinct clinical improvement; semisolid food was taken easily; the weight and strength had increased. At his own request the patient left the hospital September 21; prior to his discharge he had been taking general ward diet. Arrangements were made to continue the radium therapy.

Treatments were given October 16 and 23. On October 16 a note was made: "The shadow of the radium tube is seen to lie

<sup>28</sup> Loc. cit.

<sup>29</sup> Loc. cit.

in the area of the lesion." On December 2 he returned for another exposure. The roentgenologist reported: "There is seen an obstructive lesion in the middle third of the esophagus which supports the previous roentgen-ray finding of carcinoma. This examination seems to indicate an improvement of the lesion, as the barium passed through the obstruction with much greater ease than previously noted."

He was again admitted to the hospital on December 21. Two treatments were given, December 22, 1920, and January 13, 1921. On January 21 the esophagus was dilated with a No. 29 dilator: Tight, but bulb passed without much force. Five days later, about 9.30 P.M., the patient complained of a marked burning in the abdomen shortly after taking some veronal. Pallor and weakness of the pulse came on rapidly. Death occurred at 11.50 P.M. Shortly before he expired he coughed up some bright red blood.

Autopsy, performed on the following morning, revealed a carcinoma of the esophagus, about the level of the hilum of the lung: "There is a hard mass, 6 to 8 cm. in length, about the region of the hilum of the lung. This mass encircles the esophagus." The inner surface of the esophagus showed an ulcerating area over approximately the lower half of the mass described. The upper half of the mass was hard, fibrous, with a rough inner surface without ulceration; there appeared to be well-marked fibrosis, indicating a healing process. Within the ulcerated area described there were two small perforations connecting the esophagus with the aorta. A large quantity of blood was found in the stomach.

The perforation of the aorta, rare as it is, is not the only feature of unusual interest in this case; from the practical standpoint the bearing of the autopsy findings upon the efficacy and the difficulty of successful radium therapy is even of more interest.

Radium therapy of esophageal malignancies has to contend with certain problems as yet unsolved. The disease is insidious in nature and has often invaded neighboring organs before the symptoms have become sufficiently disturbing to send a patient to the physician. Carcinoma of the esophagus spreads by continuity of tissue; far less often do metastases occur. In the patient apparently improving, with less obstruction, greater ease of swallowing, some gain in weight and strength, symptoms of pulmonary involvement often supervene or other symptoms appear, such as pain from pressure or respiratory obstruction, due to the presence of a secondary mediastinal tumor. To these causes of failure must be added the technical difficulties of the introduction and location of the radium; the diseased area must be sufficiently dilated to admit the capsule containing radium; emplacement must be controlled by fluoroscopy. It appears from the autopsy cited that one portion of an esophageal carcinoma may be treated

successfully while another portion is missed altogether. Certainly such an interpretation may be placed on these findings, though it must be admitted that the varying effect of radium might cause an irritative effect in one area, a healing one in another. Yet it seems justifiable to emphasize the former view, to point out that evidence of healing has been demonstrated in an esophageal carcinoma hand-in-hand with an actively progressive process. Fluoroscopic control does not necessarily mean treatment of the entire tumor. Under fluoroscopic control accurate measurements must be made as to the location of the tumor and its length. Finally it is not enough to insert the radium from above. Until the tumor, for its entire length, is permeable to a sufficient degree to admit the capsule, so that the capsule may be passed the entire length and redrawn into the area, to be located at different levels, we cannot feel that our technic is directed to the treatment of the accessible growth in its entirety.

**Summary.** 1. Since the publication of Knaut, in 1896, 21 cases of esophageal carcinoma with perforation of the aorta or other large vessels have been reported. Another case is added here.

2. Autopsy findings in the case here reported disclosed certain deficiencies in the application of radium therapy. Suggestions are made for more effective technic.

---

## NOTES ON STUDIES IN THE PHYSIOLOGY OF THE GALL-BLADDER.\*

BY LIONEL S. AUSTER

AND

BURRILL B. CROHN, M.D.

NEW YORK.

AN increasing interest has been shown by the medical profession in various types of non-surgical biliary drainage; the reaction of the gall-bladder and its associated structures to the application of supposed biochemical and physiologic agents has been utilized in the diagnosis and treatment of disease of this organ.

Last year we began a series of studies, anatomic and physiologic, into the nature of certain biliary phenomena alleged to occur as a result of treatment of the duodenal mucosa and the papilla

\* These experiments were performed in the Laboratory of Physiology of Cornell University Medical College. We wish to thank Dr. Graham Lusk for his kind interest and encouragement and for his courtesy in extending to us the facilities of the laboratory.



of Vater by magnesium sulphate and other agents. As a result of these studies we present the reports of a series of animal experiments upon the action of magnesium sulphate when applied to the duodenal mucosa and the papilla of Vater, the rate and character of resultant bile flow, the contraction of the gall-bladder and the question of stasis of bile in that organ.

**I. Anatomy of the Bile Passages.** The gall-bladder<sup>1</sup> is a small pyriform sac, lying obliquely on the inferior surface of the liver; it is considered generally as an embryonic diverticulum of the hepatic duct, enlarged at its extremity to act as a reservoir for bile. Its duct, the cystic duct, joins the hepatic duct to form the ductus choledochus or common bile duct; it meets the pancreatic duct at the papilla of Vater and there empties into the second part of the duodenum. The position of the organ is such that on account of the double mesial curve of the neck and the attachment of the body the fundus is lower than the point of exit of the duct into the duodenum, necessitating an upward flow of its contents if they are to be expelled.

The wall of the gall-bladder is composed of three coats: An outer coat of peritoneum, a middle coat of smooth muscle and fibrous tissue and an inner coat of mucous membrane which presents a reticulated appearance due to the plicæ or ridges into which it is thrown. There are also a number of mucous glands of fairly large size described by Luschka,<sup>2</sup> who found from three to twenty of these glands in the gall-bladder. They are lined by long cylindrical cells giving the appearance of being ciliated cells. Holmes<sup>3</sup> describes a series of mucous glands scattered throughout the whole mucosa of the bladder and ducts.

The muscular coat is one of more than ordinary interest in connection with the function of the organ. Sparsely distributed unstriated muscle fibers are interlaced with fibrous tissue in this layer; most of the muscle bundles run longitudinally, a few transversely. These fibers are irregularly continued in the corresponding coat of the duct and at times seem to be thickened in an attempt at sphincter formation; this is especially noticeable near the junction of the cystic and hepatic ducts, as first described by Tobien.

At the opening into the duodenum, however, the papilla of Vater is found. This structure is of peculiar interest to us from an anatomic and physiologic standpoint on account of its known definite sphincteric function and its part in the control of bile flow. Our first real knowledge concerning the existence of a definite muscular mechanism at this point we owe to Oddi,<sup>4</sup> who described what he thought to be an individual set of muscular fibers surrounding the terminal portion of the common bile and pancreatic ducts. While earlier anatomists indicated the existence of such a mechanism the maceration experiments of Oddi on the

terminal ducts and papillæ of animals demonstrated existence of a set of circular muscle fibers which have since been named after him. The fibers had their origin in the circular fibers of the duct. As the duct entered and traversed the wall of the intestine the bundles were seen to thicken and lengthen, throwing out lateral fibers which mingled with the longitudinal and circular fibers of the intestinal wall, thus apparently forming "points of support" for the duct in its course. The resulting sphincter-like formation was declared by Oddi<sup>5</sup> to be separate and distinct from the intestinal musculature. This structure was seen to be especially developed in the sheep, dog, ox and pig. He showed, moreover, that the tone of the sphincter was such that it had a resistance of 50 mm. Hg (675 mm. water), which exceeds the normal secretory pressure of bile by 475 mm. of water. .

Hendriksen<sup>6</sup> in his observations upon the dog, cat, rabbit, and guinea-pig confirmed the findings of Oddi and was furthermore able to demonstrate the existence of an anatomical sphincter of similar nature in man.

We have been able to demonstrate without difficulty the existence, in dogs and in man, of circular bands of smooth muscle fibers surrounding the common bile duct in its course through the intestinal wall. By the study of microscopic sections these transversely arranged bundles are seen to be continuations of the previously described scanty musculature of the gall-bladder and the first and second portions of the common duct. In the third portion, such as described by Oddi and Hendriksen, they were seen to lengthen and thicken and become more numerous, but at no point do we see the formation of a compact distinct muscular bundle conforming to our conception of a true sphincter such as, for example, the sphincter of the pylorus, the compressor urethræ, the sphincter ani, etc.

Our observations upon the microscopic sections prepared from three dogs and three human specimens indicate that the muscular fibers of the sphincter are scanty, widely separated and diffuse and are at no time continuous. It is our impression that there is a fusion of the fibers of the intestinal muscularis with the corresponding layer of the duct which goes to make up the muscular apparatus of the papilla. That there is, however, distinct sphincteric action will be shown in a later discussion of the mechanism and function of the papilla.

The anatomic structure of the gall-bladders of dogs and man are similar.

That the gall-bladder is not essential to the well-being of the individual is seen from the normal lives led by persons after complete cholecystectomy. Likewise there are no ill effects noted in cases of congenital deformities of the gall-bladder, in which there may be partial septa or other changes. The presence of

two distinct gall-bladders has been recorded, and Gay<sup>7</sup> writes of 19 cases of complete absence of the gall-bladder in man. Schachner also cites 7 cases of congenital absence of the gall-bladder. Wilder<sup>8</sup> in discussing the slight physiologic importance of this organ and its lack of universal occurrence gives the instance of its presence in one of two animals of the same family—the fowl, whereas the pigeon has none. The gall-bladder likewise is lacking in the horse, mule, ass and elephant. (Rolleston<sup>9</sup>.)

Oddi and others, particularly Rost,<sup>39</sup> however, speak of a “compensatory” dilatation of the ducts following cholecystectomy.

With the exception of Gray,<sup>1</sup> who states that the gall-bladder is innervated by a branch from the celiac plexus, the writers of text-books of anatomy are rather vague concerning the nerve supply of the organ. A great amount of work has been done in this field, however, the outstanding feature of which is a disagreement as to the specific nature of the impulses passing to the organ.

Perhaps the earliest report on the subject is given by Oddi,<sup>10</sup> who claims for the sphincter special spinal-cord ganglion centers which regulate its tone. The location of this center he places, in dogs, at the level of the first lumbar segment. The mechanism he regards as an inhibitory reflex. Meltzer<sup>42</sup> in his studies upon contrary innervation and inhibition comments on a system of crossed innervation for the gall-bladder and sphincter, a system which would cause a contraction of the gall-bladder simultaneous with a dilatation of the sphincter, and *vice versa*. The application of the law of contrary innervation calls for a double innervation, splanchnic and parasympathetic, to the bladder and papillary muscle. It is presumed that the vagus contains motor fibers for the sphincter and inhibitory fibers for the gall-bladder. During digestion the pair of fibers in the splanchnic are brought into play and are supposed to cause the expulsion of the bile from the gall-bladder. Thus the same stimulus that traversed the splanchnic system to cause contraction of the gall-bladder would simultaneously relax the sphincter; or, travelling through the vagus system, would contract the sphincter and relax the gall-bladder.

Physiologists are not convinced about the experimental data upon which this theory rests. Doyon<sup>41</sup> in extensive experiments on stimulation of the peripheral end of the splanchnics found contraction of the gall-bladder and the bile ducts.

The contraction of the ducts, moreover, may produce complete obliteration at least at one point. On stimulation of the central end of the splanchnics he found relaxation of the sphincter. Doyon says that he never saw these two results produced simultaneously but presumes that they occur. Excitation of the peripheral end of the vagus was usually without effect. In one dog the author noted a contraction of the sphincter.

Bainbridge and Dale,<sup>12</sup> on the other hand, covering the same ground more than eleven years later, came to conclusions diametrically opposed to those just cited. Following the Doyon technique they noted upon section of both vagi and splanchnics an increase of pressure transmitted by the balloon in the gall-bladder (from 15 cm. of water to 50 cm.). They found that the "invariable result of faradizing the splanchnic nerve was relaxation of the gall-bladder." Stimulation of the efferent end of the vagus in the thorax gave rise to contraction of the gall-bladder. By means of a balloon in the gall-bladder, rhythm and tonus were demonstrated by all the foregoing authors. Contractions of the gall-bladder were evidenced by rise of manometric readings in an instrument connected with the balloon. Okada<sup>13</sup> also reports rhythmic contractions of the organ. A clear-cut demonstration of the law of crossed innervation, so far as its application to the gall-bladder is concerned, has, however, not yet been seen.

*Physiology of the Gall-bladder.* That the gall-bladder is a functioning organ which operates in a definite and characteristic manner has been upheld by physiologists generally for many years. The unanimity of opinion held by the writers<sup>14</sup> of standard text-books and reference-books is so striking as to suggest the complete absence of any attempt on the part of these authors to verify by actual observation the description of the mechanism as handed down from one author to the other.

The gall-bladder is held by all to be a reservoir for the storage of bile which is continuously secreted by the liver; such secretion is kept for intermittent periodic discharge into the intestine only during the active digesting period of the individual's day. According to the present conception, in the fasting state, bile passes down the hepatic duct and is shunted off into the gall-bladder, where it remains. Upon the passage of acid chyme from the stomach into the duodenum a reflex mechanism is excited whereby the papilla of Vater is relaxed, the wall of the gall-bladder contracts and the bile stored there is ejected into the duodenum along with an increased flow of liver bile.

Mann<sup>15</sup> emphasizes two other functional possibilities of the gall-bladder—secretion and the regulation of flow, in addition to the reservoir action.

That there is a definite tone to the sphincter and to the gall-bladder itself has been shown by many observers. Freese,<sup>16</sup> Judd and Mann,<sup>17</sup> Okada<sup>18</sup> and others hold a brief for the contractility of the organ and the sphincter, but that this contractile power is small and weak is generally agreed. As a matter of fact the musculature of the wall is so sparse that we found it impossible in dogs to obtain by strong direct faradic stimulation even the slightest contraction visible to the eye or sufficient to expel any

of the contents.\* The effect of drugs on the contractility and tonicity of the isolated gall-bladder has, however, been worked out by Lieb and McWhorter.<sup>19</sup> These authors found an increase in tonus due to myoneural parasympathetic stimulation with pilocarpin and physostigmin and a relaxation with atropin and adrenalin. Other drugs, too, showed varying effects.

The secretion and excretion of bile is a subject which is dismissed in all too cursory a manner by most text-books. Although some authors declare that the carbohydrate fraction of a meal has but little if any effect upon bile flow, they place great emphasis upon the activating property of the acid chyme of the stomach, in some cases regardless of its constituents. The stimulation of bile expulsion given by dilute HCl was shown in 1880 by Rutherford.<sup>20</sup> Okada<sup>21</sup> bears this out by his experiments with hydrochloric acid, in which he induced a bile flow by its application. He further studied the effects of cholagogues, noting marked positive effects with peptone, bile, bile salts, sodium salicylate, chloral, salol, pilocarpin and nicotin.

Voit<sup>46</sup> first noted the variations in bile flow during digestive processes. Perhaps the best study of the effect of foodstuffs, however, is that of Bruno,<sup>22</sup> who determined that not all foodstuffs are active in stimulating bile flow. As a result of a series of painstakingly detailed experiments with a Pawlow fistula in dogs he concludes that there is no psychic secretion of bile. The flow ceases as soon as the stomach is empty. The arrival of bile in the intestine is determined by the digestion of food in the stomach. The progress of the excretion of bile is more or less typical for the type of nourishment taken. The reaction of the duodenal contents, moreover, does not play the role of exciting this secretion. Water by itself did not excite the bile flow nor did albumin alone. The arrival of bile in the intestine, Bruno says, is dependent upon the chemical action of the products of digestion of albuminous bodies. Starch is not an excitant, but if meat powder is added a flow is obtained. Fats show a marked positive action. Extractives such as Liebig's meat extract show a specific action.

Bayliss and Starling<sup>23</sup> have shown that secretin acts upon the liver in a manner similar to that by which it induces the flow of pancreatic secretion. The contact of the HCl with the duodenal mucosa activates a hormone substance, secretin; they noted the absorption of this product into the blood stream and the subsequent effect of secretory stimulation of the liver cells by the secretin.

Fleig<sup>24</sup> observed an acceleration of bile flow in chloralized dogs after the introduction of oil into the duodenum.

If the gall-bladder is to act as a reservoir or flow regulator for

\* The strength of current used (six dry cells with an inductorium) was sufficient to cause, when applied to any part of the stomach or to the small or large intestine, a distinct segmental tonic spasm.

bile in transit its contents should not vary materially in composition from the material excreted directly from the liver. Moreover, to fulfil one of the functions attributed to it, that of secretion, it must have a secretory mechanism. That it has a secretory, and possibly an absorbing, function is undoubted, but not for the secretion of bile. Anatomically the only secreting tissue seen in the wall of the bladder are the mucous glands of Luschka, mentioned above. These glands, and the lining epithelium, may, however, have some excretory function, such, for example, as the excretion of toxic substances and chemicals. F. C. Mann's<sup>25</sup> work in the production of chemical cholecystitis practically specific after the intravenous injection of Dakin's solution is interesting in this regard. Of great interest are the differences in composition of the "liver bile" and the "gall-bladder bile."

Hammarsten,<sup>26</sup> Rosenbloom,<sup>27</sup> Hoppe-Seyler and Yeo and Herroun have investigated the quantitative relationships of the constituents of bladder bile and bile from a biliary fistula. The demonstrations are definite in their evidence concerning the greater concentration of the bladder bile over the so-called liver bile, Hammarsten giving the total solids in bladder bile as about eight times that of liver bile. During its stay in the gall-bladder the bile loses a large amount of water and has added to it mucin and albuminous material. Rous and McMaster<sup>28</sup> in a recent study have also given attention to the differences in quality of these two varieties of bile. They further showed that the inspissation of bile in the gall-bladder may proceed with great rapidity. This has its bearing upon the concentration of cholesterol and the subsequent formation of gall-stones. For the latter, however, there must be long-continued stasis, which, if the claims for the functions of the gall-bladder are true, is normally well-nigh impossible in an actively eating and digesting individual.<sup>29</sup>

Hawk<sup>30</sup> puts the amount of normal bile secreted by an adult man during twenty-four hours at from 500 to 1100 cc according to various estimates. Comparing this relatively large output with the normal 30 cc capacity of the gall-bladder, Mann suggested that in no animal could the gall-bladder contain more than 5 per cent of the bile secreted in twenty-four hours, and in most cases only 1 per cent. The plausibility of this remark becomes thus apparent.

*Clinical Aspects.* About four years ago Meltzer<sup>31</sup> published an article in which he discussed the basis of our conceptions regarding the innervation of the gall-bladder and its contractile mechanism. In this article he dilated upon the function of the sphincter at the ampulla of Vater and the interrelation between the contracting gall-bladder and the sphincteric action, as has been described earlier in this paper. Applying the facts made known about the "law of contrary innervation," he invoked this

principle to explain the physiologic coördination of contracting musculature and relaxing sphincter. Meltzer took a step forward and suggested that occasional types of jaundice, such as catarrhal and emotional jaundice, could be caused by disturbances in the carrying out of these coördinated nervous reflexes. He suggested an abnormal rigidity or passivity as the possible cause. He made the practical therapeutic suggestion that a concentrated solution of magnesium sulphate introduced into the duodenum through a duodenal tube might by causing a relaxation of a badly functioning sphincter at the papilla tend to relieve the jaundice.

Lyon,<sup>32</sup> in adopting the suggestion of Meltzer, carried the argument a step further. If magnesium sulphate relaxes the sphincter, then by the law of contrary innervation causes simultaneous contraction of the gall-bladder with the consequent expulsion of its contents. By collecting the fluid in the duodenum after such a saline lavage he proposed a diagnostic test for disease of the gall-bladder based on a study of the amount, character, cytology and bacteriology of these contents under normal and abnormal conditions. He has reported also a characteristic return of differently colored specimens of bile after magnesium sulphate lavage. By means of these color differences he claimed to be able to designate the various parts of the gall tract from which the bile flowed in succession—duct, gall-bladder, hepatic ductules.

That the publications of Lyon have aroused a good deal of speculation and interest in the medical profession is evidenced by the accumulation of a large amount of literature on the subject in the past three years. There have been many papers confirming in effect the claims of Lyon. On the other hand, Einhorn,<sup>44</sup> Reiss, Crohn, and Radin<sup>45</sup> and others have presented evidence against accepting the idea that the dark "B" bile extracted from the duodenum after magnesium sulphate lavage comes from the gall-bladder. At this writing, moreover, there appears the report of the striking observations of Dunn and Connell,<sup>35</sup> who, experimenting with a duodenal fistula in a person after cholecystectomy, obtained the same results as described by Lyon, albeit the gall-bladder had been removed. The stimulation of flow was seen even after the application of the solution at a point distant from the papilla (rectum) and likewise after the passage of the magnesium sulphate through the stomach.

**II. Experimental Studies.** In the following experiments normal dogs were used, some in the fasting and some in the digesting state, as indicated under such experiment.

**Anesthesia.** The animals were anesthetized with a solution of chloretone in Mazola oil injected intraperitoneally, the dose being gauged to give complete surgical anesthesia according to the weight of the animal. We chose chloretone rather than ether, chloroform or morphin on account of its easy handling, its lack

of side action and excitement stage, and, as far as we could determine, the absence of any pharmacologic or physiologic action of the drug which might in any way invalidate the observations on the gastrointestinal system.

*Operations.* All operations were carried on in a warm room with due precautions against interference with normal function on account of shock or trauma. All exposed portions of the animal during laparotomy were covered with cloths wet with warm physiologic saline solution. In cases requiring duodenotomy, periods of from fifteen minutes to half an hour were allowed before manipulations and observations were made; this was done in order to eliminate any inhibitions due to trauma occasioned by incisions.

1. *Action of Magnesium Sulphate.* A series of eight dogs were experimented with in order to test out the "specific" action of magnesium sulphate when applied to the duodenal mucosa in the region of the papilla of Vater. Laparotomy was performed and 2 to 5 cc of a solution of methylene blue in 0.9 per cent saline solution were injected into the gall-bladder of the animal in order to differentiate between bladder bile and liver bile. Three of the dogs in this series were used after fasts of over twenty-four hours. The others were fed either before the start of the experiment or an hour previously.

Observation of the gall-bladder immediately after laparotomy and before injection showed moderately distended gall-bladders in all of the dogs except one which showed a flaccid bladder. The flaccid non-distended bladder was seen in a fasting dog.

After a fifteen minute wait the duodenum was incised at the site of the opening of the bile duct. In all but two animals, one fasting and one digesting, there was noted a slow flow of bile soon after opening the duodenum. This was also true of the two other fasting dogs of the series which showed a fairly continuous, though scanty bile flow from the papilla.

In no case was there any evidence of the methylene blue in the intestine. After a wait of from fifteen to thirty minutes the site of the papilla was gently irrigated with a warm 25 per cent solution of magnesium sulphate in water. The gall-bladder and papilla were closely observed during intermittent irrigations made over periods averaging three hours for each animal. Between irrigations the duodenal area was washed with normal saline solution to avoid the protracted action of the magnesium sulphate, thus approximating the siphoning out of the solution in the clinical method. In one case where no flow was observed upon opening the duodenum a flow of bile was induced by the application of the sulphate solution. In the other cases an apparent further relaxation of the papillary sphincter and an increased flow of bile into the duodenum was noted. *In no case was any of the methylene blue bile from the gall-bladder seen to appear in spite of the apparent*



*stimulation of liver bile.* McWhorter<sup>32</sup> had demonstrated a lowering of pressure in the common bile duct of dogs of from 50 to 100 mm. after magnesium sulphate had been applied to the ampulla; no result was seen after peptone solution.

The experiments with methylene blue were controlled by the use of two animals injected with a suspension of carmine powder and one injected with a suspension of pulverized charcoal. In all cases at the conclusion of the experiment the patency of the ducts was demonstrated by exerting very slight digital pressure upon the gall-bladder. This resulted in every instance in the immediate expulsion of the contents of the gall-bladder into the duodenum, staining the mucosa intensely by the methylene blue or producing marked and unmistakable evidence of coloring matter in the cases of the carmine or charcoal suspensions.

Thus it is seen that although the application of magnesium sulphate to the duodenal mucosa at the papilla of Vater has the effect of stimulating bile flow it does not empty the gall-bladder of its contents. The flow of bile direct from the liver indicates that it is not necessary for the bile to go to the reservoir of the bladder before its excretion into the intestine. This experiment further explains the circumstance cited by Hatcher and Eggleston<sup>34</sup> of the rapid recovery of ouabain excreted in the bile in the intestine of a rat within four minutes after completion of injection.

2. *Effect of Substances Other than Magnesium Sulphate.* We wished to ascertain whether the relaxation of the musculature and the flow of bile was due to the specific effect of magnesium as maintained by Meltzer, or whether the salt action of the sulphate radical or any salt itself could produce the same effect.

First, we noted that the application of magnesium sulphate to the duodenal mucosa often produced a local peristaltic contraction of the intestinal wall. If this contraction had been due to the magnesium radical rather than to the salt action, it may perhaps be explained by reference to the work of Ralph Lillie, of A. G. Mayer and of Stockard<sup>45</sup> at the Tortugas Laboratory at Naples about twelve years ago, in which the investigation of properties of Mg, Na, K and other substances showed a contraction of smooth muscle and similar types of cells by Mg, whereas striped muscle showed the characteristic relaxation described by Meltzer.\*

\* In this connection it is necessary to review the observations of Meltzer regarding magnesium, and to clearly differentiate what Meltzer and Auer<sup>36</sup> actually saw from what Meltzer conjectured. Most of the work of these authors upon magnesium was done either by intravenous injection or by nerve blocking. In the latter set of experiments<sup>40</sup> it was observed that blocking of a peripheral nerve (e. g. sciatic) could be brought about by wrapping the nerve in a cloth saturated in strong magnesium solution. In the set of abdominal experiments it was noted<sup>40</sup> that after intravenous injection of magnesium sulphate there was an absence of the violent peristaltic contractions originated by sections below the medulla, by physostigmin or ergot as well as such as are seen as an agonal phenomenon. The only attempts directly to observe the effect of a magnesium salt when applied in the intestinal mucosa is mentioned in the article in the Archives for Internal Medicine.<sup>41</sup> In this article it was noted that

Second, not only was the stimulation of bile flow seen with magnesium sulphate, but a similar increase in biliary excretion was noted after the local application of a solution of peptone, of sodium sulphate, sodium phosphate, bile and sodium glycocholate. No stimulation was seen after the application of sodium chloride or potassium or sodium hydroxide.

3. *Contractile Power of the Papillary Muscle.* By drawing the finger over the papilla, by faradic stimulation or by the use of chemical irritants, it was seen in numerous cases that the "sphincter" reacted with a contraction which promptly closed the duct. A high degree of irritability was evidenced, since even the slightest mechanical stimulation sufficed to contract the papilla. An interval of between ten to thirty seconds usually elapsed during which time the muscle of the papilla remained contracted so as to cause a characteristic elevation. Relaxation then took place and the bile flow was resumed. Not only the papilla but the surrounding segment of the duodenum responded to the stimulus. If the stimulus (faradic) was strong enough the whole intestinal segment was tonically contracted.

We attempted in seven cases to cause a contraction of the musculature within the gall-bladder wall by the use of the faradic current, but no success greeted our efforts although we used as many as eight dry cells connected to an inductorium, set to give the maximum stimulus (enough to cause violent tonic contraction of any muscular region to which it was applied on the animal). Thus a current which caused a tonic segmental contracture of stomach or duodenum or small or large intestine failed to evince a response from the gall-bladder.\*

peristalsis ceased in a loop of intestine when the lumen was filled with magnesium sulphate solution. It will however be noted that no specific details of such experiments are given, nor can one conclude whether Meltzer regarded such a local intestinal action as due to a nerve block or a direct ionic paralyzant action on the muscle cell. Above all, in view of the great confidence which is justly and properly reposed in all the statements made by the late S. J. Meltzer, it behooves us to remember that he does not at any time quote any experiment in which magnesium was applied to the papilla of Vater; his was a "suggestion," not a "fait accompli." Statements in the literature crediting Meltzer and Auer with having performed any experiments in which magnesium salts were applied to the papilla and its action noted upon either the papilla or the gall-bladder are erroneous. Furthermore, the hypothesis that magnesium sulphate provides its effect upon the bile flow after absorption into the portal or general circulation (Einhorn) is not voided by any experiments of Meltzer and Auer. In fact Meltzer definitely states that magnesium sulphate is readily absorbed from the lumen of the intestine and can by means of the circulation produce its general effect in paralyzing muscular activity.<sup>41</sup> This phenomenon has been studied also by Hertz, Cook and Schlesinger.<sup>47</sup>

\* Several physiologists have succeeded in demonstrating that the gall-bladder wall of a dog is capable of giving small rhythmic contractions, both tonal and in response to faradic stimulation. (Doyon, Okada, Burton-Opitz). These experiments were performed usually with a distended balloon in the gall-bladder; such a procedure by stretching or perhaps over-stretching this hollow viscus may likely produce such tonal variations in a smooth muscle organ as to simulate, when recorded upon a kymograph, contractions. To date, however, we believe that no one has seen a gall-bladder actually contract with a forceful constriction of its fibers sufficient to expel its contents.

4. *Nervous Control of Gall-bladder Contractility.* In two instances efforts were made to contract the gall-bladder by stimulation of the vagus and splanchnic nerves. These experiments were not attempts to parallel the work of Doyon or Bainbridge and Dale, but were done merely in our own interest without elaborate preparations such as made by the two authors quoted. (Introduction of balloon and manometer, etc.) In neither case could we excite any visible gall-bladder contraction, although in one case the methylene blue was discharged into the intestine. This, however, we attribute to the fact that strong faradic stimulation of the right vagus nerve caused general abdominal contractions of intestines, diaphragm, stomach, etc., with movement and pressure of the liver and other organs upon the distended gall-bladder. The expulsion of the discolored bile in this case was mechanical rather than nervous.

5. *Gall-bladder Stasis during Normal Activity and Digestion.* Using ether anesthesia, three dogs were operated upon aseptically; the gall-bladders of these animals were injected with suspensions of carmine powder or charcoal. The abdomen was sutured, surgical dressings applied and they were permitted to recover from anesthesia and play about in the animal room. These dogs were fed with fat meat, biscuits and water in order to provide a diet well balanced in protein, carbohydrate and fat. They showed no ill effects upon recovery from the operation and were seen to eat their food with relish. The operations were performed on different days. The animals were permitted to live for twelve, twenty-four and seventy-two hours respectively, at which times they were killed by intracardial injection of a massive dose of strychnin in order to produce immediate death without violent agonial muscular contractions. They were immediately examined and search was made throughout the entire intestinal canal for evidences of discolored bile indicating discharge from the gall-bladder. In none was any trace of carmine or charcoal found. The bile ducts were patent and free from obstruction, as shown by slight digital pressure causing the expulsion of a gush of dye-colored bile from the gall-bladder, unmistakably discoloring the intestinal wall. There was no evidence of any inflammatory lesion or septic condition resulting from the laparotomy or the gall-bladder injection. Active digestion was in progress at the time each of the dogs were killed. No evidence of artificially colored gall-bladder bile was found outside of the bladder itself, although the intestinal wall in the upper region was markedly stained with normal yellow liver bile.

In a further experiment a dog under the same circumstances was observed after the lapse of one week. During the seven days intervening between the operation and the autopsy the dog was fed with a mixed carbohydrate-fat-protein diet. A cutaneous

infection at the site of the incision was observed, but no peritoneal involvement was present.

Examination of the gall-bladder at autopsy showed a normal bladder, half filled with light brown bile and no evidence of the carmine suspension injected a week previously. Examination of the contents and mucous membrane of the colon showed evidences of the carmine powder which had probably been expelled into the intestine one or two days previously. Carmine was not demonstrated in the feces of the terminal colon or sigmoid.

Bile stasis in the gall-bladder of the dog has thus been shown up to seventy-two hours concurrent with active digestion of a balanced diet and with unmistakable evidence of *a free flow of liver bile*. The attempt to extend the observation of this phenomenon to a week showed that by that time the gall-bladder had emptied itself. Apparently there is some sort of uncertain and irregular movement of bile from the sac, though our observations thus far have not confirmed the existence of the supposed ejaculatory mechanism.

6. *Movement of Bile into the Gall-bladder.* In seeking a substance with which to test the movement of liver bile into the gall-bladder we chose phenol-tetrachlor-phthalein, originally studied pharmacologically by Abel and Rowntree<sup>37</sup> in 1909 and described as a test for functional activity of the liver in 1913 by Rowntree, Horwitz, and Bloomfield.<sup>38</sup> This substance was freshly prepared in an alkaline solution by boiling under a reflux condenser. On account of experiences with animals which demonstrated to us its toxic nature when given in solutions not sufficiently dilute we administered the dye to chlorotomized dogs, by the injection into the femoral vein of 50 cc of a 0.5 per cent solution over a period of fifteen minutes.

A return of the dye in the bile ejected from the papilla was noted usually within ten to fifteen minutes and could be ascertained positively by placing about 1 cm. of the bile collected in a test-tube, diluting with 10 cc of water and then adding a few drops of concentrated sodium hydroxide. The presence of the dye was indicated by the appearance of an intense reddish-purple color. At the same time the dye could be demonstrated in specimens of bile independently aspirated from the gall-bladder.

We repeated the experiments upon a dog, after tying off the cystic duct with a ligature at the neck of the gall-bladder. Injection of the phthalein was accomplished as described above; bile collected from the papilla in fifteen minutes showed the presence of dye being excreted. Periodic aspiration of small amounts of the contents of the gall-bladder were negative for the dye during a two-hour observation period. This showed that phenol-tetrachlor-phthalcin was not secreted from the gall-bladder wall.

It further demonstrated that there is an inward flow of liver bile into the bladder.

7. *Filling of the Gall-bladder in a Normal Dog.* An attempt was made to determine the rate of filling of the empty gall-bladder. After laparotomy and duodenotomy the content of the gall-bladder was expressed into the duodenum by pressure upon the organ. The bile continued to flow throughout the period of observation of one hour. The gall-bladder was aspirated by means of a hypodermic syringe at fifteen minute intervals after the digital emptying. In all 7 cc of bile were obtained by this mode of aspiration, 3 cc the first time 2 cc the second and 1 cc at each of the subsequent two aspirations.

The gall-bladder was here seen to begin filling soon after emptying, the rate of filling being, however, very slow.

At a subsequent experiment the same procedure was adopted; in this instance no bile collected in the gall-bladder during a period of two hours, though there was a constant slight flow from the papilla. (These last observations should call for more complete and more numerous investigations.)

**Conclusions and Summary.** 1. Anatomically the gall-bladder wall contains scanty musculature of poor contractile power.

2. A typical distinct anatomic sphincter at the papilla of Vater was not demonstrated, although there is definite sphincteric action. The papilla shows an extremely high degree of irritability in the chloretonized dog.

3. The nervous control of the gall-bladder is uncertain. We have been unable to produce definite contractions by nervous stimulation and there are conflicting reports of such phenomena observed by others.

4. The application of concentrated solutions of magnesium sulphate to the duodenal mucosa and papilla of Vater of the dog caused a stimulation of bile flow. It did not cause an expulsion of bile from the gall-bladder.

5. The flow of bile into the duodenum is not inhibited by the existence of a fasting state or empty non-digesting stomach.

6. In the fasting state the gall-bladder is not necessarily distended. In the digesting state during copious bile flow the gall-bladder was observed to be filled.

7. Application of magnesium sulphate to the duodenal mucosa caused a stimulation of peristaltic contraction.

8. Bile flow may be induced by the application to the mucosa of peptone, sodium sulphate, sodium phosphate,  $\frac{N}{10}$  hydrochloric acid and bile and sodium glycocholate. No stimulation of flow was seen after water, NaCl,  $\frac{N}{10}$  NaOH.

9. Strong faradic stimulation of the gall-bladder wall did not contract the organ.

10. Stasis of the gall-bladder contents was observed in normally digesting dogs up to three days. The gall-bladder was found to have emptied itself in one week.

11. The gall-bladder wall does not excrete phenol-tetrachlorophthalein, though the liver does. Although there must be some movement of the bile into the gall-bladder, as evidenced by the presence of this substance in some cases in which the cystic duct was not tied off, how the material passes from the sac and under what conditions is unknown to us.

12. The filling of the emptied gall-bladder is an irregular and a slow process.

**Concluding Remarks:** After contemplating this series of experiments it would appear that we should reconsider the view of the gall-bladder as an actively functioning organ that rhythmically fills and empties itself under the stimulus of digestion. That the liver bile has normal free ingress into the gall-bladder has been demonstrated. That an enormous inspissation or concentration of bile in the bladder takes place, with the addition of a mucous element, has further been agreed upon and more recently emphasized by Rous and McMaster. But how or at what rate emptying occurs remains open to consideration. Most of the work by physiologists has been done with biliary or duodenal fistulæ; the variations in the bile flow in respect to digestion have been rather presumed to follow and to depend upon the filling and emptying of the gall-bladder.

We are inclined to the belief that the flow of bile originates in the liver and sweeps down the ducts into the duodenum disregarding in main part the gall-bladder. Such variations in bile flow and concentration as occur originate in the liver in answer to the various degrees of food stimuli.

It does not seem that the gall-bladder as an active organ enters into the physiology of bile excretion. Certainly it does not seem to have an ejaculatory mechanism or the proper musculature for such a function in the same light as one speaks of the urinary bladder or of the seminal vesicles. The outflow from the gall-bladder appears to be in the nature of an overflow incontinence. Under pathologic conditions one knows that this organ is capable of great distention, acting at such times as an exhaust vent or safety valve to relieve intraductal pressure. Such a function is complementary to its great capacity to concentrate the bulk of bile by dehydration and inspissation.

#### REFERENCES.

1. Text-books of Anatomy: Cunningham, Gray, Piersol, Morris.
2. Luschka: *Anatomie des Menschen*, 1863, 2, 256.
3. Holmes: *Lancet-Clinic*, 1911, 106, 678-684.

4. Oddi: D'une disposition sphinctere speciale, etc., Arch. Ital. de biol., 1887, 8, 317.
5. Oddi: Monitore zoologico Ital., 1894, 5.
6. Hendricksen: Johns Hopkins Hosp. Bull. 1898, 9, 221.
7. Gay: Trans. Chi. Path. Soc., 1902, 5, 108.
8. Wilder: History of Human Body, Holt 1909, p. 295.
9. Rolleston: Diseases of the Liver and Gall-bladder, MacMillan, 1912.
10. Oddi: Sul centro spinale dello sphintere del choledoe., Arch. de physiol., normal et path., 1894, p. 931; Sul centro, etc. Lo Sperimentale, 1894, 48, 180.
11. Doyon: Arch. de physiol. norm. and path., 1894, 6, 19.
12. Bainbridge and Dale: Jour. Phys., 1915, 33, 138.
13. Okada: Jour. Physiol., 1914, 49, 457.
14. Text-books of Physiology: Howell, Starling, Tigerstedt, McLeod, Am. Text-book of Phys., Luciani, Bayliss, Also Barker, Medical Record, 1907, 62, 555.
15. Mann: New Orleans Med. and Surg. Jour., 1918, 71, 80.
16. Freese: Johns Hopkins Hosp. Bull., 1905, 16, 235.
17. Judd and Mann: Surg., Gynec. and Obst., 1917, 24, 437.
18. Okada: Jour. Physiol., 1915, 50, 42.
19. Lieb and McWhorter: Jour. Pharm. and Exper. Therap., 1915, 7, 83.
20. Rutherford: Trans. Royal Soc. of Edinburgh, 1880, 29, 29.
21. Okada: Loc. cit.
22. Bruno: Arch. d. sc. biol., St. Petersburg, 1899, 7.
23. Bayliss and Starling: Brit. Jour. Physiol., 1902, 28, 348; Starling, Human Physiology, Lea and Febiger, 1915, p. 716.
24. Fleig: Arch. internat. d. physiol., 1914, 286.
25. Mann, F. C.: Ann. Surg., 1921, 73, 54.
26. Hammarsten: Text-book of Physiol. Chemistry, 1904, p. 276.
27. Rosenbloom: Jour. Biol. Chem., 1913, 14, 24.
28. Rous and McMaster: Proc. Soc. Exper. Biol. and Med., 1920, 17, 215.
29. Tigerstedt: Lehrb. der Physiol. des Menschen, 1920, p. 389.
30. Hawk: Physiological Chemistry, 1918, p. 207.
31. Meltzer: AM. JOUR. MED. SCI., 1917, 153, 469.
32. Lyon: Jour. Am. Med. Assn., 1919, 73, 980.
33. McWhorter: Surg., Gynec. and Obst., 1921, 32, 124.
34. Hatcher and Eggleston: Jour. Pharm. and Exper. Therap., 1919, 12, 432.
35. Dunn and Connell: Jour. Am. Med. Assn., 1921, 77, 1093.
36. Meltzer and Auer: Am. Jour. Physiol., 1906, 16, 4.
37. Abel and Rowntree: Jour. Pharm. and Exper. Therap., 1909, 1, 231.
38. Rowntree, Horwitz and Bloomfield: Johns Hopkins Hosp. Bull., 1913, 24, 327.
39. Rost: Mitteilung a. d. grenzgb. Med. u. Chir., 1913, 26, 710.
40. Meltzer and Auer: Am. Jour. Phys., 1906, 17, 313.
41. Meltzer: Arch. Int. Med., 1915, 15, 956.
42. Meltzer: Medical Record, (June 7), 1902, 61, 888.
43. Voit, Carl: Beitr. z. Biol. Festgabe Anat. u. Physiol. Th. L. W. von Bischoff, Stuttgart, 1882.
44. Einhorn: New York Med. Jour., 1921, 113, 8.
45. Reiss, Crohn and Radin: Jour. Am. Med. Assn., 1921, 76, 1567.
46. Meltzer: Inhibitory and Anesthetic Properties of Magnesium Sulphate, Med. Rec., 1905, 68, 965;
47. Hertz, Cook and Schlesinger: Proc. Roy. Soc. Med., 1908, 11, No. 2; Therap. and Pharm., p. 21.
48. Stockard: Personal communication.

## CHEMICAL CHANGES OF THE BLOOD DURING IMMUNIZATION.

BY G. L. ROHDENBURG, M.D., O. F. KREHBIEL, M.D.,

AND

A. BERNHARD, B.S.

NEW YORK.

(From Columbia University, Institute of Cancer Research, F. C. Wood, Director.)

IN the present paper the chemical changes occurring in the blood during the process of immunization are considered. In order to make a clear presentation of the subject, it has been found necessary to review in considerable detail some previously published experiments, both our own and those of others. The experiments referred to are studies in carbohydrate physiology, the investigation of which, based upon the microchemical examination of the blood, dates from the work of Jacobsen. Jacobsen<sup>3</sup> found that the ingestion of definite amounts of glucose was followed by a temporary increase in the amount of blood sugar, and that this increase began about 5 minutes after the ingestion, reached its maximum in about 45 minutes and subsided in about 120 minutes. Further studies of this phenomenon made by other investigators<sup>4 5 6 7 8 9 10</sup> have shown that the reaction may be completed in a shorter period of time or may extend over a longer space than 120 minutes and that in some diseased conditions the reaction varies, *i. e.*, the blood-sugar values either rise to a higher level or are less marked than the normal.

Changes in the blood sugar similar to those just described also follow the injection of adrenalin<sup>11</sup> and other internal secretions<sup>12</sup> as well as the injection of protein, peptone and some of the protein-split products,<sup>13 14</sup> certain mineral salts<sup>15</sup> and at least one mineral acid.

Subsequent experiments carried out in this laboratory confirmed the occurrence of hyperglycemia after the injection of peptone and demonstrated that any protein parenterally introduced disturbs the blood-sugar equilibrium,<sup>1</sup> the disturbance manifesting itself by either a temporary decrease or an increase of the blood-sugar concentration. The experiments, furthermore, brought out the fact that similar changes in the blood sugar continue to occur with each subsequent injection of the specified protein (*e. g.*, typhoid bacilli) until the power of the organism to produce antibodies against the protein injected is exhausted, whereupon further injections fail to cause disturbance of blood-sugar equilibrium. It was also found that changes in blood sugar do not follow the subcutaneous injection of autologous protein in normal animals, but do occur when homologous protein is used. This phenomenon



led to the observation that, in contrast to normal animals, about 75 per cent of mice bearing spontaneous malignant tumors fail to show disturbance of blood sugar after the injection of homologous protein.

A protein having been injected into the selected animal the method of determining a disturbance of the blood-sugar equilibrium was as follows.\* Just before the injection and again forty-five minutes and one hundred and twenty minutes thereafter, blood was withdrawn and its sugar content determined; the lowest of the three values thus obtained was subtracted from the highest and the

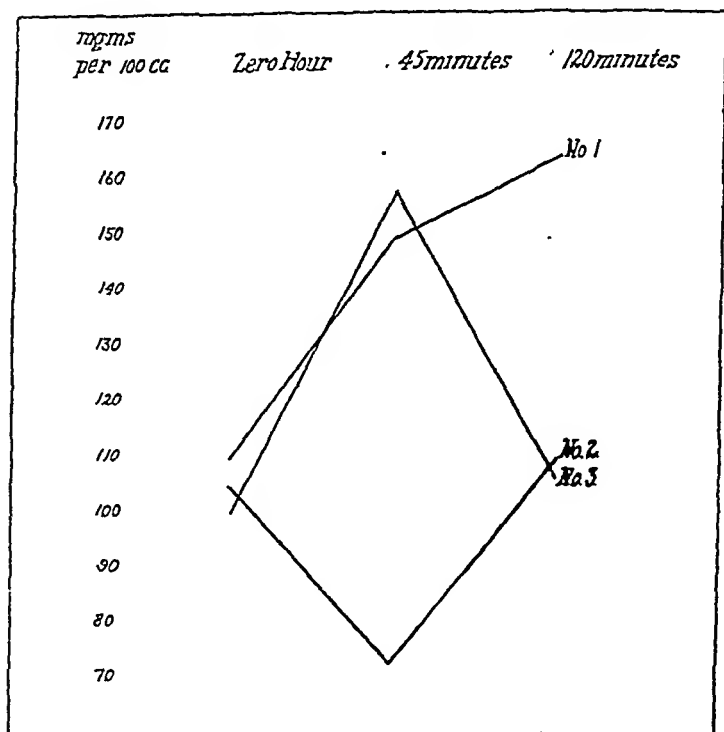


CHART I

variation between these two values represented the disturbance of sugar equilibrium in milligrams. Three methods were used in determining the blood-sugar values in animals, the Epstein, the Kleiner and the Folin (micro). In our hands the Folin method has been found to be the most satisfactory. Inasmuch as in the animal work the comparative but not the actual values are of importance, it is not necessary to use any given method in making the sugar

\* In all of our experiments the animals were kept on a fixed diet, and were invariably starved for a period of twelve hours antedating the experiment. They received no food until the last specimen of blood had been withdrawn.

estimations. It is, however, essential that one method be used throughout any one experiment and that all determinations be carefully done by the same person, who should be experienced in blood-sugar work.

In the course of our observations three types of reaction were noted; and while they have been described elsewhere,<sup>8</sup> they are again illustrated in Chart I.

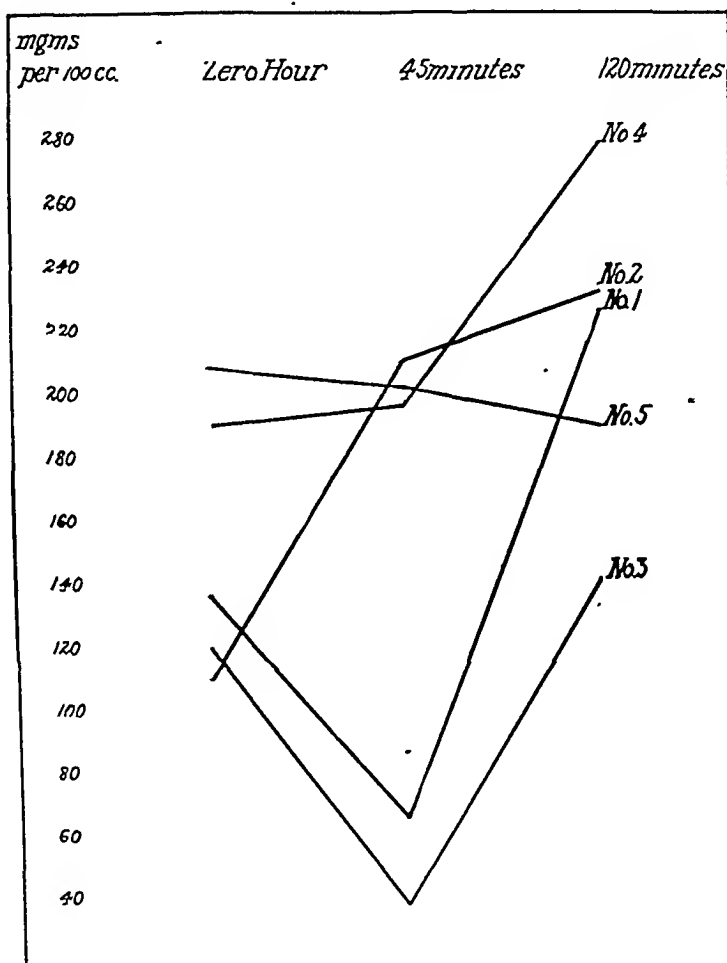


CHART II

Such variations in the reaction must have some significance. It may be, as has been suggested,<sup>16</sup> that in every instance there is an increase in blood-sugar concentration, but that its maximum may occur at different time intervals, and that after the maximum increase there is a lowering of the blood-sugar values below the preinjection value, and finally a return to the preinjection level. In other words, in some instances the reaction is completed very quickly, while in others it occurs slowly. Blood taken at the designated time intervals may, therefore, catch different phases

of the reaction. However, further study of variations in the type of reaction brought out the fact that the same animal, after successive injections of the same protein, reacted differently after each injection, and that the intensity of the reaction also varied. Chart II presents observations on a rabbit injected repeatedly with the same dose of washed sheep red cells. Chart III presents

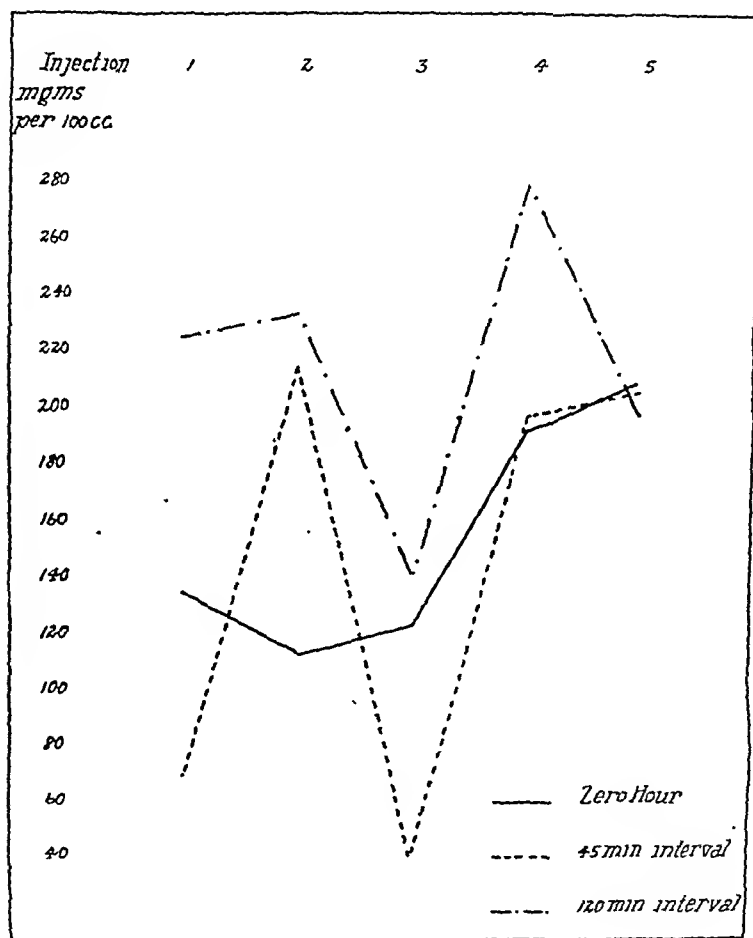


CHART III

the same data in different form. Here the values for the zero hour and the forty-five and one hundred and twenty minute intervals are shown as curves and it is evident that these curves gradually approach one another. In other words, the difference between the high and the low blood-sugar values for each successive test becomes less and less. This successive diminution in the disturbance of the sugar values is striking when presented in the form employed in Chart IV.

In accordance with the foregoing it seems logical to conclude that the disturbance of blood-sugar equilibrium which follows the injection of a protein is not to be judged by the type of reaction but by the degree of disturbance as measured in milligrams.

In view of the disturbances of blood sugar just described it seemed important to undertake further investigations in order to determine if other elements in the blood might not undergo similar disturbances. A further study was therefore undertaken in which the changes in blood sugar, total blood solids, total blood nitrogen and the hydrogen-ion concentration of the blood after protein injection were considered. Particular interest was centered in the possible changes in the total blood nitrogen, since it has been recently suggested <sup>17 18</sup> that there exist nitrogen-storage centers

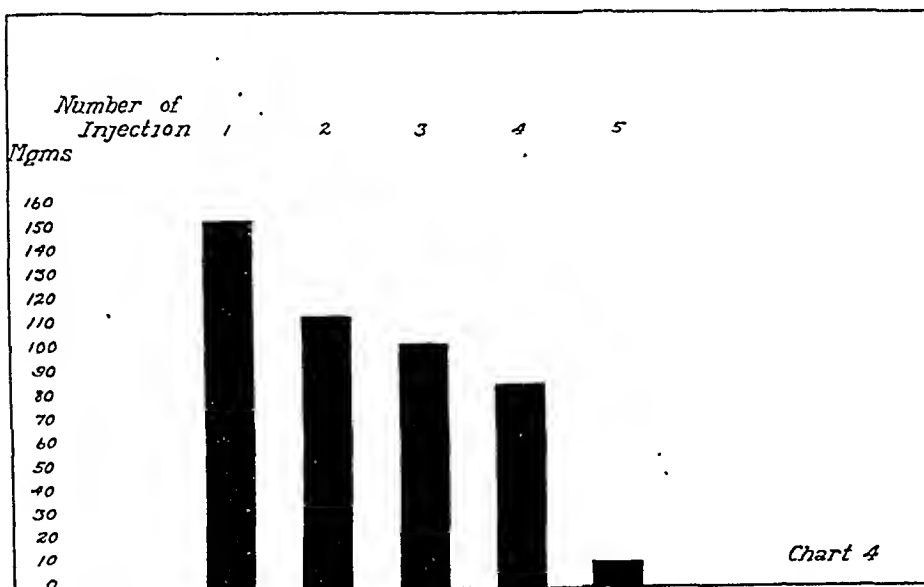


CHART IV

analogous to the sugar-storage centers, and it was thought possible that changes in the total blood nitrogen analogous to the blood-sugar changes mentioned in the previous paragraphs might be demonstrated.

Six rabbits, after having been placed on a fixed diet and starved for a period of twelve hours before each test, were injected in varying ways with typhoid bacilli prepared as follows: Three agar slants were incubated for twenty-four hours; each slant was washed off with 3 cc of physiologic salt solution and the suspension was heated to 60° C. for one hour. The injections were made at weekly intervals: Rabbits 1 and 2 were injected intravenously: First dose, 0.5 cc; second dose, 1 cc; third dose 1 cc. Rabbits 3 and 4 were injected intraperitoneally, the doses being

1 cc, 2.5 cc, and 2.5 cc. Rabbits 5 and 6 were injected subcutaneously the dosage being the same as for rabbits 3 and 4.

Just before each injection, and again one hour after injection, blood was withdrawn, and on the specimens so obtained the following estimations were made: Blood sugar by the Kleiner method;<sup>19</sup> total blood nitrogen after the method of Folin;<sup>20</sup> total blood solids as described by Meyers and Fine;<sup>21</sup> hydrogen-ion concentration according to the method of Marriott, Rowntree and Levy.<sup>22</sup> Titers of the serum for agglutinins against typhoid bacilli were also made on blood taken before injection. Before any injections were given, control determinations of sugar, total nitrogen, total solids, hydrogen-ion concentration and agglutinin were made in order to note the changes which would occur in a one-hour interval without the injection of protein.

It will be noted that in this experiment the time periods at which the blood specimens were taken were changed to the zero hour and the sixty-minute interval instead of the previously described three intervals. This was done because interest centered not in the type of reaction encountered, but in the comparative degree of disturbance of equilibrium produced by the injection.

After the last typhoid injection the protein was changed to a 50 per cent suspension of washed sheep red cells in physiologic saline solution. In all the animals the fourth injection, 3 cc of the sheep red-cell suspension was given subcutaneously. The change of antigen was made in order to determine whether, when typhoid antigen had lost its power to induce disturbance of sugar equilibrium, another antigen could still call forth the phenomenon.

The numerical data of this experiment are given in Table I, and these data as averaged for the entire group are graphically shown in Chart V. In general the chemical changes noted were a gradual decline in the concentration of sugar and of nitrogen in all of the animals during the course of the experiment.

A comparison of the behavior of the various fractions of the blood in relation to the development of the agglutinin titer is of interest. The experiment embraces a group of animals subjected to a common type of stimulus. As in all biologic phenomena the individual members of the group have responded in different degree, though not in different manner, to this stimulus. Of the animals injected, two developed agglutinins in increasing strength, two developed agglutinins in increasing strength but very slowly, and two developed agglutinins which reached their maximum with the second injection and then receded. In analyzing a biologic phenomenon in order to determine some broad, general rule, it seems justifiable to consider the experimental group as a whole rather than as individuals, for in no biologic phenomenon with which we are familiar do all of the members of a group necessarily react alike in degree, though they do in manner. For this reason

Animal number.	Dose injected.	Substance injected.	Typhoid agglutinins, titer.	Preinjection.				Postinjection.				Degree of disturbance of equilibrium.			
				Sugar. Mgms.	Nitrogen. Mgms.	Solids. Gms.	Ph.	Sugar. Mgms.	Nitrogen. Mgms.	Solids. Gms.	Ph.	Sugar. Mgms.	Nitrogen. Mgms.	Solids. Mgms.	Ph.
I.	0	0	0	120	2900	17.900	7.0	140	2400	17.890	7.1	+20	500	10	.1
	0.5 cc	Typhoid	400	110	2000	15.600	7.3	110	2100	18.600	6.6	0	100	3000	.7
	1 cc	Typhoid	1800	110	2000	15.700	7.2	100	2000	.....	7.2	-10	0	.....	0
	1 cc	Typhoid	2000	90	2100	11.500	7.4	100	2000	16.900	7.4	+10	100	5400	0
	3 cc	Sheep cells	....	60	1900	14.800	7.0	100	1950	15.300	7.6	+40	50	500	.6
II.	0	....	0	120	1900	.....	7.3	100	2000	17.100	7.4	-20	100	.....	.1
	0.5 cc	Typhoid	10	80	2000	17.300	7.0	110	2200	18.400	6.7	+30	200	1100	.3
	1 cc	Typhoid	400	90	2000	14.000	7.4	60	2000	13.800	6.6	-30	0	200	.8
	1 cc	Typhoid	1000	100	1900	14.600	7.2	90	1900	14.500	7.2	-10	0	100	0
	3 cc	Sheep cells	....	90	1700	16.900	6.8	90	1700	16.300	7.6	0	0	600	.8
III.	0	....	0	120	2000	17.700	7.3	120	2000	17.100	7.4	0	0	600	.1
	1 cc	Typhoid	0	110	2200	18.000	7.1	110	2200	17.000	7.4	0	0	1000	.3
	2.5 cc	Typhoid	20	110	2000	14.500	7.5	80	2000	15.300	7.5	-30	0	800	0
	2.5 cc	Typhoid	100	100	2100	17.400	7.5	90	2100	16.600	7.5	-10	0	800	0
	3 cc	Sheep cells	....	90	1650	15.300	7.4	120	1600	.....	7.0	+30	50	.....	.4
IV.	0	....	0	120	2200	.....	7.1	100	2000	17.000	6.6	-20	200	.....	.5
	1 cc	Typhoid	200	70	2000	18.000	6.6	120	2000	20.000	6.8	+50	0	2000	.2
	2.5 cc	Typhoid	1000	90	2000	16.300	7.4	70	2000	17.500	6.8	-20	0	1200	.8
	2.5 cc	Typhoid	500	70	1800	16.300	7.4	80	1800	15.900	7.2	+10	0	400	.2
	3 cc	Sheep cells	....	70	1850	17.600	7.5	70	1860	.....	7.3	0	10	.....	.2
V.	0	....	0	100	2300	18.000	7.6	120	2160	18.000	7.4	+20	140	0	.2
	1 cc	Typhoid	0	120	2000	17.000	7.4	90	2000	17.000	6.6	-30	0	0	.8
	2.5 cc	Typhoid	1000	110	2000	17.600	7.3	100	2000	18.000	7.3	-10	0	400	0
	2.5 cc	Typhoid	100	90	1900	15.900	7.8	90	2000	15.700	7.5	0	100	200	.3
	3 cc	Sheep cells	....	70	1700	15.000	7.3	70	1660	16.500	7.7	0	40	1500	.4
VI.	0	....	0	100	2180	19.000	7.1	100	2200	20.000	7.3	0	20	1000	.2
	1 cc	Typhoid	200	120	1900	.....	7.4	130	2000	.....	7.1	+10	100	.....	.3
	2.5 cc	Typhoid	200	100	2200	17.000	7.2	110	2200	15.600	7.3	+10	0	1400	.1
	2.5 cc	Typhoid	500	120	1900	16.400	7.8	120	1870	14.500	7.5	0	30	1900	.3
	3 cc	Sheep cells	....	70	1700	15.600	7.4	90	1800	15.500	7.4	+20	100	100	0

All values on 100 cc basis.

the degree of disturbance of equilibrium in any one of the factors which have been considered has been averaged for the entire group. These averaged results are presented in Chart V.

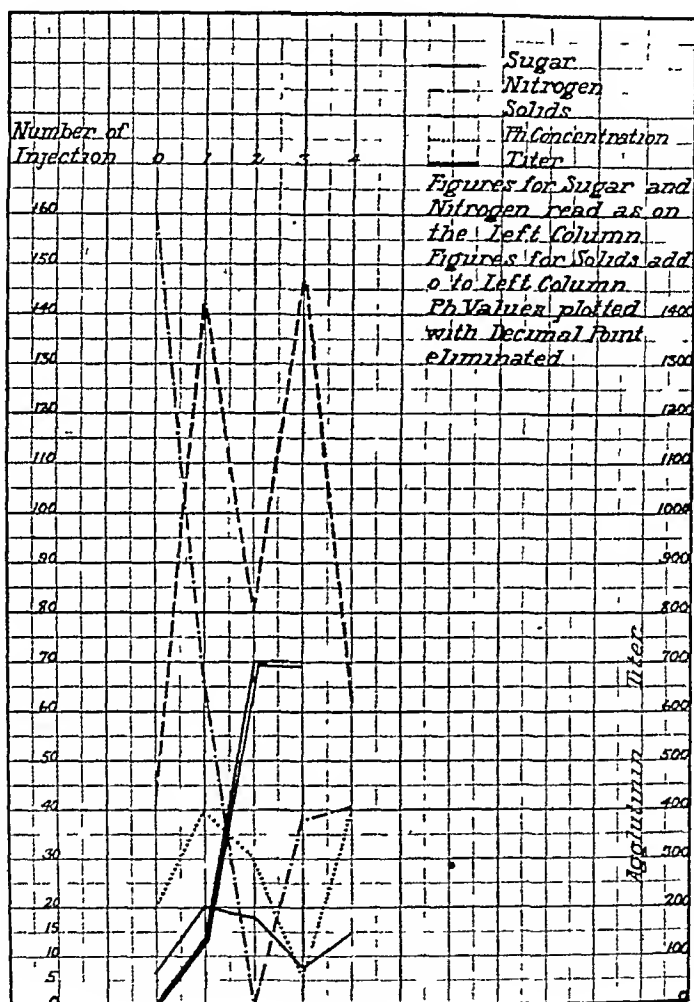


CHART V

*Agglutinins.* Inasmuch as the experiment was planned to study the relation of various chemical changes in the blood to the development of antibodies the development of agglutinins became the standard of comparison. Before any injections were given, none of the animals had agglutinins for the *Bacillus typhosus*. Seven days after the first injection the averaged titer was 1 to 135, while seven days after the second injection it reached 1 to 700, remaining at this figure seven days after the third injection;

in other words the maximum agglutinin-producing power of this group resulted in a serum having the power of agglutinating typhoid bacilli when diluted 1 to 700.

*Blood Sugar.* Control examinations made before any injections were given showed a fluctuation of sugar equilibrium of 6.6 mgm. This is probably not a real disturbance but represents the limit of technical accuracy of the method employed. The first injection resulted in a disturbance of 20 mgm., the second in a disturbance of 18 mgm., the third in a disturbance of 6.6 mgm. At the same time that the titer of agglutinins had attained its maximum disturbances of blood sugar greater than that observed without injection (*i. e.*, greater than the limits of analytical accuracy) ceased. When, however, the antigen injected was changed from typhoid bacilli to sheep red cells there followed a variation of 15 mgm.

*Hydrogen-ion Concentration.* The disturbances of hydrogen-ion equilibrium are recorded in Chart V only in the first decimal place of the logarithm  $P_H$ . As is shown in the chart, these disturbances of equilibrium run parallel to the disturbance of blood-sugar equilibrium. What has been stated concerning the relationship between agglutinin development and blood-sugar equilibrium applies equally well to the disturbances of hydrogen-ion concentration.

*Nitrogen.* The control examinations (*i. e.*, without injection of any type) made at the designated time intervals showed a disturbance of the total nitrogen equilibrium of 160 mgm. per 100 cc of blood. This is a marked disturbance and cannot be explained by the analytic limitations of the method used. After none of the subsequent injections was there as marked a degree of disturbance of nitrogen balance as was observed without injection, neither was there any demonstrable relationship between disturbance of nitrogen equilibrium and the development of antibodies.

*Total Solids.* Each injection of typhoid bacilli caused a greater disturbance of the total solids equilibrium than was observed in the control determinations; and in this instance also there was no demonstrable relationship between disturbances of the total solids and the development of antibodies.

The results of the foregoing experiment seem to indicate that while disturbances of the blood-sugar, hydrogen-ion concentration, total nitrogen and total solids do occur with each injection of the protein used, only those of the blood sugar and hydrogen-ion concentration bear any relationship to the development of antibodies.

In a second experiment the work of the first was repeated except for the antibody titration. In this experiment the antigen used was a 50 per cent suspension of washed sheep red cells in physiological saline, subcutaneous injections, three in number, of 2 cc each, being given. The injections were made at weekly intervals and



three rabbits formed the experimental group. In this experiment, the data of which are given in chart form only (Chart VI) the same cycle was observed as in the first experiment. The disturbances of total nitrogen and total solids equilibrium followed no definite sequence, while the disturbances of equilibrium of both

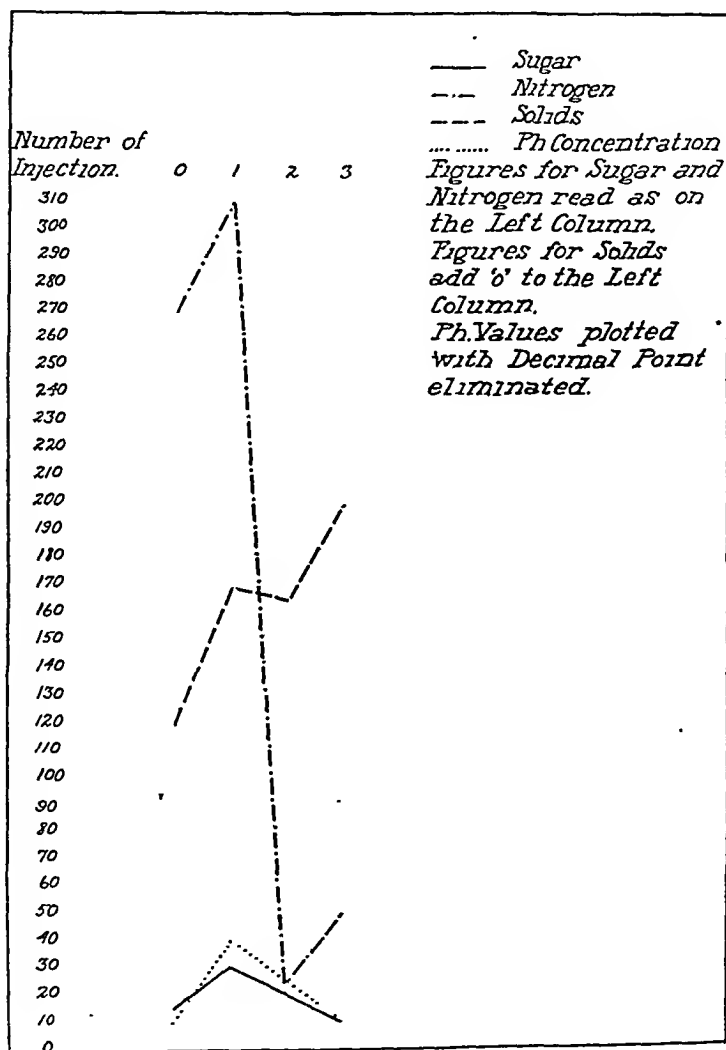


CHART VI

the blood sugar and hydrogen-ion concentration ran parallel and followed a definite sequence.

In a third experiment blood-sugar estimations were made on two rabbits after repeated injections of a 50 per cent suspension of washed sheep red cells in physiologic saline solution. The



Here the relationship between disturbances of blood-sugar equilibrium and antibody formation is strikingly evident.

Rabbit 1 showed a fluctuation of blood-sugar equilibrium of 3 mgm. before any injections were given. This disturbance is probably not a true one, but, as in our first experiment, represents the limit of analytical accuracy of the method of blood-sugar determination. The first injection of red cells produced a disturbance of 32 mgm. and resulted in the development of lysins demonstrable in a dilution of 1 to 500. The second injection of red cells disturbed the blood-sugar equilibrium only 6 mgm. and increased the lytic power of the serum but slightly. The third injection created a disturbance of blood-sugar equilibrium of 13 mgm. and caused the lytic titer to rise to 1 in 2000. The fourth and the fifth injections created no disturbance of blood-sugar equilibrium, neither did they cause any increase in the strength of lytic substance present in the serum. In marked contrast to this the sixth injection caused a disturbance of 40 mgm. in the blood-sugar equilibrium and at the same time the lytic titer rose to 1 in 5000, while the seventh injection caused no disturbance of equilibrium and did not produce any further rise in lytic titer.

Rabbit 2 ran much the same course as did rabbit 1. The second, third and fourth injections failed to disturb the sugar equilibrium more than 7 mgm., and did not cause any increase in the strength of the lysins in the serum, while the fifth, sixth and particularly the seventh injections produced marked disturbances of the blood-sugar equilibrium, and again at the same time the lytic power of the serum rose to the high titer of 1 to 10,000. In other words, when the injected antigen failed to disturb the sugar equilibrium then no increase in antibody formation (in this instance lysins) occurred.

Inasmuch as certain salts have been shown by Underhill and his co-workers to interfere with the glycemie disturbance which follows the injection of adrenalin, it might be maintained that our results are due to the saline constituents of the material injected. That this is not true is shown by the following experiment:

Control blood-sugar estimations (Folin-Wu micro-method) were made on a group of six rats without injection, the time intervals chosen being the zero hour and the sixty-minute interval. These control determinations, when averaged for the group, showed a variation of 6 mgm. in the blood-sugar level. The same group when injected with 0.5 cc of a mush of rat spleen in physiologic saline solution gave an averaged disturbance of 15 mgm. The same animals were then injected with varying amounts of a saline solution prepared so as to contain the following salts in grams per liter: potassium ehloride, 2.062; potassium sulphate, 0.205; potassium monophosphate, 1.202; sodium monophosphate, 0.457; sodium chloride, 3.622; calcium phosphate, 0.193; magnesium

phosphate, 0.177. As is shown in Chart VIII, when this saline solution was injected in the proportion of  $\frac{1}{170}$  of the body weight the averaged degree of disturbance was 16 mgm. Such an injection is equivalent to 4230 cc in a 150-pound man. Smaller injections gave progressively less-marked disturbances of blood-sugar equilibrium.

In another series of six rats injections of 0.5 cc of a physiologic saline solution produced a disturbance, as averaged for the group, of 6 mgm. of blood sugar. In the proportion used in our previously described protein experiments, therefore, the influence of the saline solution can be disregarded, because saline injections affect the blood-sugar equilibrium only when injected in a proportion of 1 to 1000 of the body weight or more. The maximum disturbance of blood-sugar equilibrium occurred in the rabbits injected with protein with the initial injection, that is, the one containing

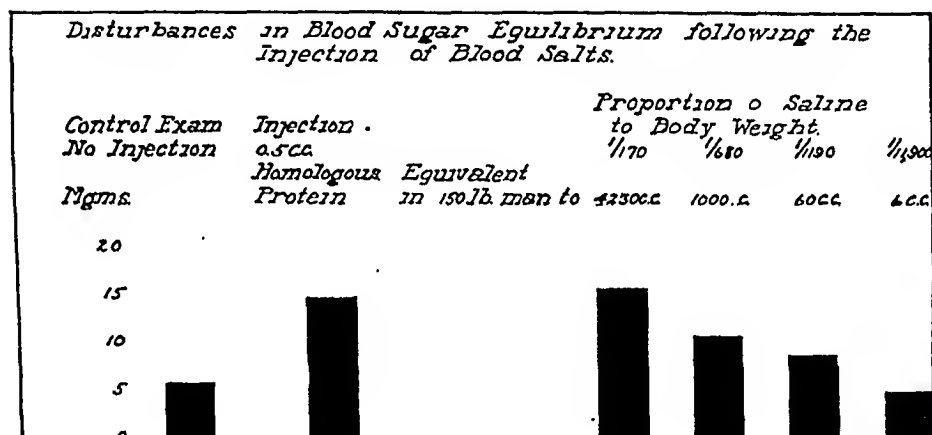


CHART VIII

the smallest amount of saline solution; while later injections which contained larger amounts of saline solution failed to disturb the blood-sugar equilibrium. If the saline were the controlling factor the greatest disturbance of blood-sugar equilibrium would follow the last and not the first injection.

A phenomenon as easily aroused as is the disturbance of blood-sugar equilibrium is probably under a very complex physiologic control, and one is led to suspect the endocrines as regulators.

That the disturbance of blood-sugar equilibrium which follows the injection of protein has a different significance from that of the disturbance which follows the injection of adrenalin is shown by the following experiment:

Sixty normal mice and an equal number of normal rats were injected with 0.125 cc of adrenalin hydrochloride (1 to 1000) solution, blood-sugar estimations (Epstein method) being made just before and again sixty minutes after the injection. An equally large group

of rats and mice bearing transplanted tumors were injected and examined in a similar manner. The averaged degree of disturbance of sugar equilibrium for each group is presented in Chart IX. While mice show a greater disturbance of sugar equilibrium than do rats there is no significant difference between tumor-bearers and normal animals.

When, however, the degree of disturbance of equilibrium following injection of homologous protein is compared in normal mice and in mice bearing spontaneous tumors, it is at once apparent that the disturbance of blood-sugar equilibrium which follows the injection of adrenalin is of different significance from that which follows the injection of homologous protein. In the experiment

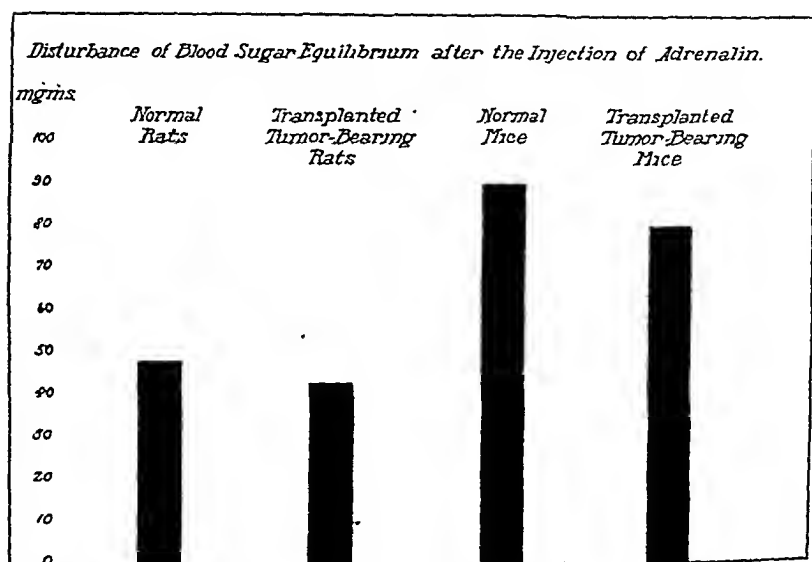


CHART IX

which demonstrates this fact, 28 normal mice and 28 mice bearing spontaneous tumors were injected on different occasions with 0.5 cc of homologous protein derived either from mouse-spleen or mouse-tumor tissue, and on a third occasion were injected with a similar dose of autologous protein derived either from their own spleen or their own spontaneous tumor. Just before and again sixty minutes after such injections blood-sugar estimations were made (Epstein method) and the degree of disturbance of equilibrium estimated in milligrams. The averaged data of this experiment are given in Chart X. It will be noted that autologous protein fails to disturb the sugar equilibrium, for variations of 2 to 6 mgm. are within the limits of analytical error of the method. When



Strictly speaking, however, this is not an autologous protein, for the present host merely furnishes the food supply for a group of cells which have originated in another animal. The averaged data for this experiment are given in Chart XI. Both groups showed the same degree of disturbance of equilibrium after the injection of heterologous protein, the actual values being 46 mgm.

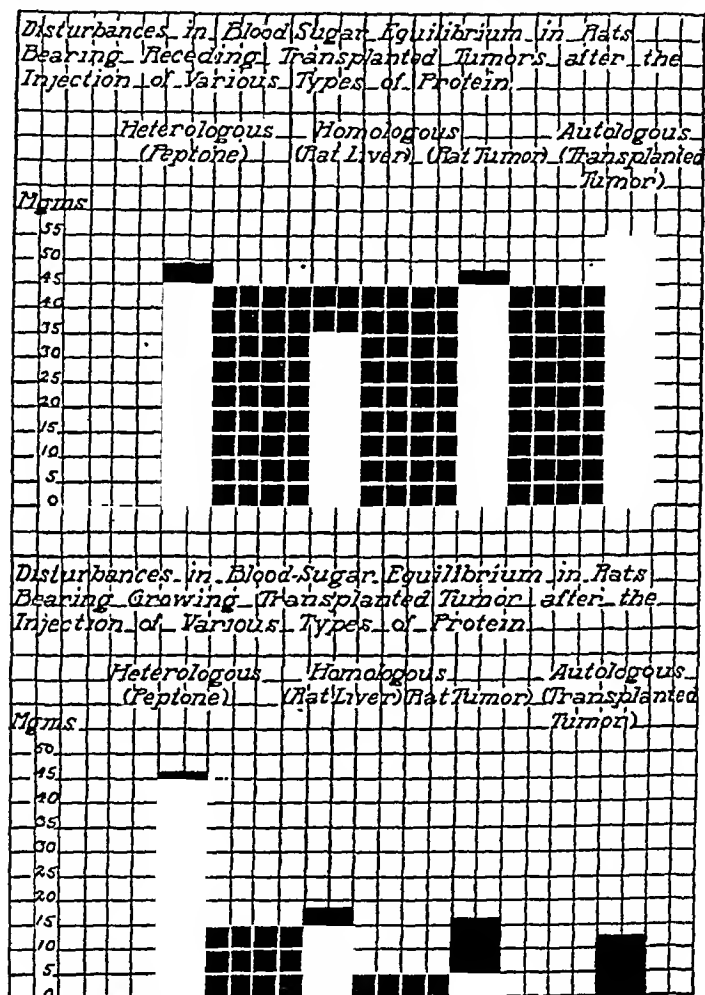


CHART XI

for the progressively growing tumors and 49 mgm. for the spontaneously receding tumors. However, when homologous protein was injected the animals bearing receding tumors showed a greater degree of disturbance than did the group bearing growing tumors, and of the two types of homologous protein used the greatest degree of disturbance of equilibrium was caused by the rat tumor

protein in animals bearing receding tumor. The disturbance of equilibrium in animals bearing progressively growing tumors was approximately one-third as great as that in those bearing receding tumors. The most marked differences between the two groups occurred when the animals were injected with autologous transplanted tumor, for in this instance the animals whose tumors receded reacted approximately five times as markedly as did those whose tumors grew. In marked contrast to the differences of behavior of these two groups when injected with homologous protein is the similarity of their behavior when injected with heterologous protein.

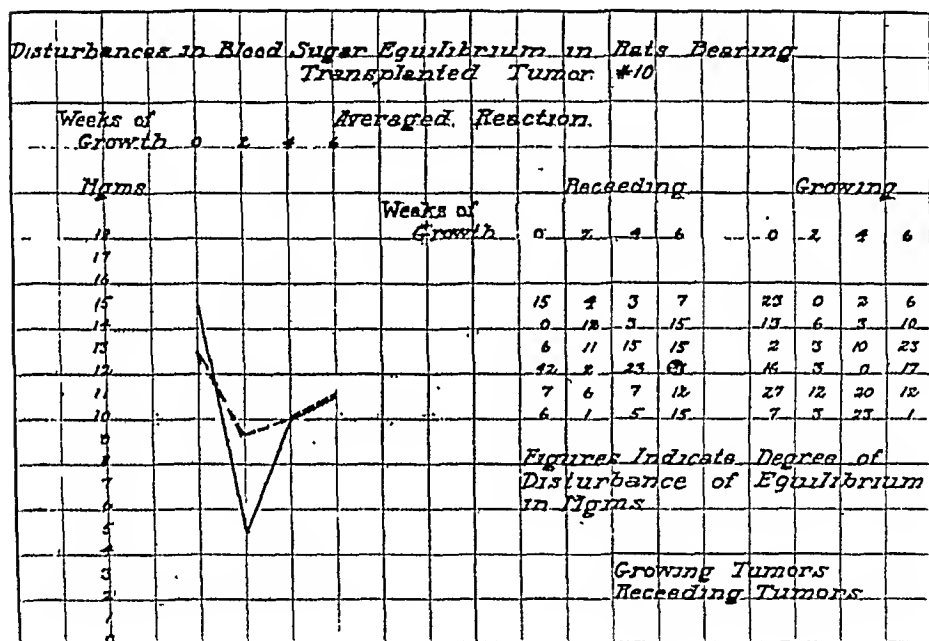


CHART XII

In another experiment the disturbance of blood-sugar equilibrium was studied under somewhat different conditions. Twelve rats were inoculated with rat tumor 10. Just before inoculation and at intervals of two weeks thereafter, for six weeks of tumor growth, blood-sugar determinations were made in these animals just before and again sixty minutes after injection of 0.5 cc of homologous protein (rat spleen); the sugar determinations were made by the modified micro method of Folin and Wu. This tumor strain receded in about 50 per cent of the inoculated animals, and of some 600 spontaneous recessions which have been observed in this laboratory in this tumor strain, 95 per cent have occurred before the fourth weeks of tumor growth.

The data of this experiment are given in detail and in graphic form in Chart XII. It is evident that the group in which the



tumor receded showed a greater degree of disturbance of blood-sugar equilibrium during the period when spontaneous recession most frequently occurs than did the group in which the tumor continued to grow. Interestingly enough, both groups reacted to about the same degree before the inoculation of the tumor, both showed a marked decrease in the reaction at the end of two weeks' tumor growth and both groups reacted to the same degree after the fourth week of tumor growth.

**Summary.** 1. During the process of immunization there occur disturbances of the total nitrogen content and total solids of the blood, as well as of the blood-sugar and of the hydrogen-ion concentration. None of these disturbances except those of the blood-sugar and hydrogen-ion concentration can be correlated with the development of antibodies.

2. The repeated injection of a given antigen results in disturbance of both blood-sugar and hydrogen-ion concentration equilibrium until the point is reached where the organism has exhausted its antibody-producing powers against the specific antigen. After the antibody-producing powers have reached this phase no further disturbance of blood-sugar or hydrogen-ion concentration equilibrium occurs until the organism has recovered or unless another antigen is used.

3. The principle so outlined is applied in a study of the reactions in animal tumors, and it is shown that there is no difference between the reaction of normal mice and rats and of those bearing tumors when injected with adrenalin or with heterologous protein. However, when homologous protein is injected a large majority of normal animals and animals bearing receding tumors react to the injection with a marked disturbance of the blood-sugar equilibrium, while animals bearing spontaneous tumors or tumors which are progressively growing show either slight or no disturbance of blood-sugar equilibrium.

The application of this principle to the diagnosis of neoplasia in man is considered in another paper.

#### BIBLIOGRAPHY.

1. Rohdenburg and Pohlman: *AM. JOURN. MED. SCI.*, 1920, 159, 853.
2. Rohdenburg: *Jour. Cancer Research*, 1920, 5, 279.
3. Jacobsen: *Biochem. Ztschr.*, 1913, 56, 471.
4. Hamman and Hirschman: *Arch. Int. Med.*, 1917, 20, 761.
5. Hopkins: *AM. JOUR. MED. SCI.*, 1915, 149, 254.
6. Taylor and Hutton: *Jour. Biol. Chem.*, 1916, 25, 173.
7. Janney and Isaacson: *Arch. Int. Med.*, 1918, 22, 160.
8. Rohdenburg, Krehbiel and Bernhard: *AM. JOURN. MED. SCI.*, 1920, 159, 577.
9. McCasky: *Jour. Am. Med. Assn.*, 1920, 73, 245.
10. Friedenwald and Grove: *AM. JOUR. MED. SCI.*, 1920, 160, 313.
11. Bloom: *Deutsch. Arch. f. klin. Med.*, 1901, 71, 146.
12. Achard, Ribot and Binet: *Compt. rend. Soc. de biol.*, 1919, 82, 788.
13. Kuryama: *Jour. Biol. Chem.*, 1917, 29, 127, 139.
14. Watanabe: *Jour. Biol. Chem.*, 1918, 34, 73.

15. Underhill: Jour. Biol. Chem., 1905-06, 1, 113; 1908, 4, 395; 1911, 9, 113; 1911-12, 10, 159; 1914, 19, 119; 1916, 25, 461; 1917, 29, 127.
16. Geyelin: Proc. New York Path. Soc., 1920, N. S., 20, 3.
17. Green: Jour. Biol. Chem., 1919, 39, 435.
18. Moulton: Jour. Biol. Chem., 1920, 43, 67.
19. Kleiner: Jour. Am. Med. Assn., 1920, 74, 58.
20. Folin and Farmer: Jour. Biol. Chem., 1912, 11, 493.
21. Meyers and Fine: Chemical Composition of Blood in Health and Disease, New York, 1915.
22. Marriott, Rowntree, and Levy: Arch. Int. Med., 1915, 16, 389.
23. Folin and Wu: Jour. Biol. Chem., 1913, 12, 367.
24. Wallace and Gallagher: Lancet, 1920, 199, 2, 784.
25. Rohdenburg and Krehbiel: AM. JOUR. MED. SC., 1921, 162, 28.

## BIOCHEMICAL STUDIES IN DISEASES OF THE SKIN. II. ACNE VULGARIS.

BY OSCAR L. LEVIN, M.D.

ATTENDING DERMATOLOGIST, BETH ISRAEL HOSPITAL; INSTRUCTOR AND CHIEF OF  
CLINIC, DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, CORNELL UNIVERSITY  
MEDICAL SCHOOL AND CLINIC; ADJUNCT DERMATOLOGIST, MOUNT SINAI  
HOSPITAL; ASSOCIATE DERMATOLOGIST, MONTEFIORE HOSPITAL

AND

MAX KAHN, M.D.

DIRECTOR OF LABORATORIES AND ATTENDING PHYSICIAN, DISEASES OF METABOLISM,  
BETH ISRAEL HOSPITAL; ASSOCIATE, DEPARTMENT OF BIOLOGICAL CHEMISTRY,  
COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

(From the Departments of Dermatology and Laboratories, Beth Israel Hospital,  
New York.)

THE theories of the causation of acne vulgaris are many and the remedial agents vary with the underlying notion of its etiology. The very fact that one dermatologist is convinced that it is an infectious disease, that another is certain that endocrinopathy is the causative factor, and that still a third is assured that some dietetic disturbance is responsible, is an evidence that our knowledge of the disease is vague. The changes in the chemistry of the body present in acne vulgaris deserve much study, for it appears to us that until the knowledge of the disturbance in metabolism of this condition is clear and definite, all theories of etiology and all plans of therapy are as fallacious as they are empiric.

It is the purpose of the present communication to summarize briefly the results that we have obtained in the study of some of the metabolic phases of the body in acne vulgaris. The work is still in progress and we hope to throw some more light on the subject in the future.

**Nitrogen Retention Products in the Blood.** In Table I, it will be observed that the urea nitrogen, non-protein nitrogen and creatinin

content of the blood were determined in 12 cases. In general no abnormal figures were obtained. In those instances in which there were slight deviations from the normal figures, constitutional disorders like exophthalmic goiter and nephritis were found.

TABLE I.—NITROGEN RETENTION PRODUCTS IN THE BLOOD

Case.	Urea nitrogen.	Non-protein nitrogen.	Creatinin.
1 . . . . .	17	24	1.0
2 . . . . .	9	18	1.0
3 . . . . .	9	20	1.05
4 . . . . .	9	24	0.8
5 . . . . .	17	22	0.62
6 . . . . .	26	..	2.3
7 . . . . .	23	37	2.1
8 . . . . .	11	24	2.8
9 . . . . .	19	23	1.2
10 . . . . .	14	27	1.6
11 . . . . .	14	20	1.5
12 . . . . .	19	23	1.2

**Calcium Content of the Blood.** One year ago, Thro and Ehn reported that in acne vulgaris the calcium content of the blood (in 12 cases) showed a marked increase, the figures they obtained being from 13.6 mg. to 25.7 mg. per 100 cc of blood. In a previous paper we reported that we had failed to find an increase in the calcium content in the blood from 7 acne patients. At that time we employed the method of Halverson and Bergeim. During the past year we examined the blood from several patients with acne vulgaris for the calcium content by means of the method of Kahn and Hadjopoulos and again found no increase. Recently, Thro and Ehn reported that they found that they had used a faulty method in their previous communication. Upon using another they found quantities of calcium oxide in acne varying from 4.9 to 16.6 mg. per 100 cc of blood. They conclude, "We found that the calcium content of the blood was high in patients with very severe acne who had not been treated, but there were great variations in the amounts of calcium in the blood of acne patients."

The following method of Kahn and Hadjopoulos lends itself to the determination of calcium in small quantities of blood. By the use of this method we found no increase in the calcium content of the blood in acne cases:

To 1 cc of blood serum in a 10 cc test-tube add 4 cc of a 1 per cent solution of ammonium oxalate. Let stand for one-half to one hour and centrifuge for five minutes. Pour off the supernatant fluid. Wash the precipitate three times with distilled water, recovering the precipitate by means of centrifugalization. Add to the sediment 1 cc distilled water and transfer to a vitreosil crucible. The test-tube is washed with distilled water and the washings also collected in the crucible. The water is slowly evapo-

rated and the precipitate burnt in a strong flame until calcium oxide is formed. Dissolve the ash in 0.5 cc fiftieth normal hydrochloric acid with hundredth normal sodium hydroxide, using phenolphthalein as an indicator. The amount of calcium oxide can now be calculated.

TABLE II.—CALCIUM CONTENT OF THE BLOOD IN ACNE VULGARIS

Case.	Mg. CaO in 100 cc.	Case.	Mg. CaO in 100 cc.
1 . . . . .	8.5	9 . . . . .	8.5
2 . . . . .	9.0	10 . . . . .	12.0
3 . . . . .	9.7	11 . . . . .	10.5
4 . . . . .	11.2	12 . . . . .	9.5
5 . . . . .	8.7	13 . . . . .	11.0
6 . . . . .	8.5	14 . . . . .	10.0
7 . . . . .	7.4	15 . . . . .	11.0
8 . . . . .	8.4		

**Glycemia.** Schwartz, Heimann and Mahnken reported that there is an increase in blood sugar in cases of acne vulgaris. In another communication describing our investigations on the blood chemistry in various skin diseases we corroborated the presence of a hyperglycemia or a high normal blood sugar content in acne. As shown in Table III, we have examined the blood from 34 patients during the postabsorptive period for the sugar content according to the method of Benedict. Out of the 34 specimens examined, 18, or almost 53 per cent, showed figures of 0.1 per cent or more; while 10 of these, or almost 23 per cent, showed figures of 0.12 per cent or more.

**Glucose Tolerance.** To 24 patients with acne vulgaris on a fasting stomach were administered 100 gm. of glucose in water. The blood was drawn from the vein previous to the administration of the glucose and subsequent to it at two intervals, one of forty-five minutes and the other of two hours. The blood was examined immediately for the glucose content in all these specimens. The results are recorded in Table III.

It will be seen that the glucose curve in all the cases is quite normal. In the average individual there is (subsequent to an ingestion of 100 gm. of glucose) a gradual rise in blood sugar, so that the maximum is attained after forty-five minutes. There is then a gradual decline to normal at the end of two hours. Patients who have a poor tolerance for carbohydrates will, on the other hand, show a continuous rise in the blood sugar with no decline in a period of several hours or days, and the glucose appears in the urine. This latter curve is most suggestive of early diabetes, hyperthyroidism being excluded.

In the series of 23 cases here reported the initial percentage of blood sugar varied from 0.058 to 0.135, rose to a height varying

from 0.08 to 0.17 and gradually receded to measurements ranging between 0.06 and 0.125, yielding curves corresponding to what we would call the normal.

**Renal Glucose Threshold.** It will also be observed that 4 of the patients (17, 21, 24 and 29) showed the presence of sugar in the urine subsequent to the ingestion of the glucose. The urine from all the 23 patients was examined for sugar prior to the administration of the glucose and at intervals of forty-five minutes and two hours subsequently. Sugar was absent from all the urines before and after the administration of the glucose, excepting in the specimens from the 4 patients mentioned above. The presence of glycosuria following the administration of 100 gm. of glucose; the presence of a normal blood-sugar curve, and the absence of other symptoms of diabetes warrant a diagnosis of decreased renal glucose threshold.

TABLE III.—GLYCEMIA, GLUCOSE TOLERANCE, RENAL GLUCOSE THRESHOLD IN ACNE VULGARIS

Case.	GLYCEMIA, PER CENT.			Glucose in urine after test.
	Prior to 100 gm. glucose ingestion.	After 3 to 4 hours.	After 2 hours.	
1 . . . . .	0.1			
2 . . . . .	0.09			
3 . . . . .	0.129			
4 . . . . .	0.13			
5 . . . . .	0.08			
6 . . . . .	0.13			
7 . . . . .	0.17			
8 . . . . .	0.2			
9 . . . . .	0.13			
10 . . . . .	0.1			
11 . . . . .	0.1			
12 . . . . .	0.08	0.088	0.085	0
13 . . . . .	0.08	0.09	0.07	0
14 . . . . .	0.058	0.08	0.06	0
15 . . . . .	0.07	0.09	0.07	0
16 . . . . .	0.08	0.095	0.07	0
17 . . . . .	0.08	0.1	0.09	+
18 . . . . .	0.07	0.15	0.08	0
19 . . . . .	0.06	0.08	0.07	0
20 . . . . .	0.12	0.16	0.09	0
21 . . . . .	0.135	0.165	0.1	+
22 . . . . .	0.07	0.09	0.06	0
23 . . . . .	0.07	0.85	0.06	0
24 . . . . .	0.11	0.17	0.09	+
25 . . . . .	0.06	0.095	0.07	0
26 . . . . .	0.1	0.15	0.1	0
27 . . . . .	0.12	0.17	0.13	0
28 . . . . .	0.09	0.14	0.12	0
29 . . . . .	0.09	0.16	0.1	+
30 . . . . .	0.12	0.15	0.13	0
31 . . . . .	0.11	0.15	0.125	0
32 . . . . .	0.09	0.17	0.1	0
33 . . . . .	0.1	0.13	0.09	0
34 ! . . . . .	0.1	0.16	0.135	0

**Acidosis.** In 1919, collaborating with Schwartz and Mahnken, we concluded as a result of investigations as to the alkali reserve of the blood in 139 skin cases that a mild or moderate state of acidosis had been found sufficiently often in acne vulgaris to warrant further study. Sweitzer and Michelson, in 1920, found no marked or consistent change in the alkali reserve in this condition. They employed the Van Slyke method for determining the carbon dioxide combining power of the plasma in 6 cases, and in only 1 was there a mild acidosis. Since then we have continued our studies on acidosis in acne vulgaris in 34 cases.

In this series there was only 1 case which showed a severe acidosis. In this girl the carbon dioxide combining power of the blood plasma was 36 per cent by volume, as determined by Van Slyke's method, and the alveolar carbon dioxide was 4.6 per cent as measured by Fredricia's apparatus. The ammonia output in the twenty-four-hour urine specimen was rather high, 2.74 gm. Ten of the other patients showed a mild acidosis as determined by these methods. Several of the remaining cases showed figures of a low normal alkali reserve of the blood bordering on an acidosis.

TABLE IV.—ACIDOSIS IN ACNE VULGARIS

Case.	CO <sub>2</sub> blood.	CO <sub>2</sub> alveolar Air.	NH <sub>3</sub> gm. 24-hr. urine.	Case.	CO <sub>2</sub> blood.	CO <sub>2</sub> alveolar air.	NH <sub>3</sub> gm. 24-hr. urine.
1	50	...	....	18	56	5.3	1.3
2	54	...	....	19	..	5.2	1.63
3	54	...	....	20	62	5.6	0.95
4	46	...	....	21	..	6.0	0.86
5	40	...	....	22	..	5.8	0.75
6	68	...	....	23	56	5.8	
7	66	...	....	24	54	5.6	
8	54	...	....	25	66	5.8	1.75
9	61	...	....	26	48	5.6	2.23
10	52	...	....	27	50	5.6	1.85
11	48	...	....	28	52	5.8	1.34
12	61	...	....	29	48	5.4	1.27
13	58	5.6	0.94	30	52	5.8	1.65
14	53	5.7	0.11	31	58	6.2	
15	62	5.8	1.51	32	55	5.6	1.53
16	60	5.5	0.82	33	..	5.2	2.25
17	50	5.4	0.82	34	36	4.6	2.74

**Studies of the Feces.** The stool from 23 patients was examined for enzymes, reaction, fermentation and microscopically for food fibers. It will be seen that most feces were acid in reaction and showed marked carbon dioxide fermentation. Only 4 gave ammoniaal fermentation. The enzymes were excellent in all cases for amylase, were good in all cases save 4 for protease, and were fair or good in all cases for lipase.

TABLE V.—FECES IN ACNE VULGARIS

Case.	Reaction.	Amylase.	Enzymes protease.	Lipase.	Fermen- tation.	Food.
1	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
2	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
3	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
4	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
5	Acid	Good	Good	Fair	CO <sub>2</sub>	Meat and vegetable.
6	Alkaline	Good	Poor	Good	NH <sub>3</sub>	Much meat.
7	Neutral	Good	Fair	Good	NH <sub>3</sub>	Much meat.
8	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
9	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
10	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
11	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
12	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
13	Acid	Good	Good	Fair	CO <sub>2</sub>	Meat and vegetable.
14	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
15	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
16	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.
17	Acid	Good	Good	Fair	CO <sub>2</sub>	Meat and vegetable.
18	Acid	Good	Good	Fair	CO <sub>2</sub>	Meat and vegetable.
19	Neutral	Good	Fair	Fair	NH <sub>3</sub>	Much meat.
20	Alkaline	Good	Poor	Fair	NH <sub>3</sub>	Much meat.
21	Acid	Good	Good	Fair	CO <sub>2</sub>	Vegetable.
22	Acid	Good	Good	Fair	CO <sub>2</sub>	Vegetable.
23	Acid	Good	Good	Good	CO <sub>2</sub>	Meat and vegetable.

The Basal Metabolism in Acne Vulgaris. Magnus-Levy was the first to point out the theoretical possibilities of metabolimetry in the diagnosis and treatment of constitutional disorders. It remained for DuBois and Benedict and others in this country to succeed in making data concerning the rate of energy production of distinct clinical importance. The term "basal metabolism" designates the heat production of an individual at the lowest level of cell chemistry. The heat production is at its minimum while the individual is at complete mental and physical rest. The most practical method for determining the heat production is by measuring the amount of oxygen consumption by means of a Benedict metabolimeter, and from these data the heat production is calculated in relation to the body surface, which is determined by Du Bois's height-weight chart. The caloric value of oxygen is employed to estimate the respiratory quotient obtained. A variation of 10 per cent from the average is considered within the normal limit.

In view of the fact that acne vulgaris is generally regarded as a cutaneous complication of a constitutional disorder, and considered by some dermatologists as depending for its etiology on an endocrinopathy, we deemed it advisable to determine the metabolic rate in a series of cases. From the data that we have obtained the metabolic rate in the average acne case seems to be enhanced. To incriminate the thyroid from this alone, however, is not justifiable, for the increase in oxygen consumption is very moderate. We hope in the near future to make other endocrine studies with the aim of throwing more light on the subject.

TABLE VI.—BASAL METABOLISM IN ACNE VULGARIS

Case.	Per cent.	Case.	Per cent.
1 . . . . .	+4	12 . . . . .	-3
2 . . . . .	+5	13 . . . . .	+12
3 . . . . .	-3	14 . . . . .	+12
4 . . . . .	+10	15 . . . . .	+10
5 . . . . .	+8	16 . . . . .	+11
6 . . . . .	+9	17 . . . . .	+8
7 . . . . .	+8	18 . . . . .	+9
8 . . . . .	+6	20 . . . . .	+12
9 . . . . .	+14	21 . . . . .	+11
10 . . . . .	+12	22 . . . . .	+8
11 . . . . .	+11		

**Summary and Conclusions.** 1. We have studied the biochemical status of 38 patients with moderate and severe acne vulgaris of one to fifteen years' duration.

2. In 15 cases in which the nitrogen retention products in the blood were investigated no constant defect could be detected.

3. The calcium content of the blood in our series of cases was not increased.

4. Hyperglycemia, or a high normal blood sugar, accompanied over 50 per cent of the 34 cases studied.

5. The blood-sugar curve was normal in all the 23 patients who were studied for their carbohydrate tolerance.

6. The renal glucose threshold was decreased in 4 out of 23 patients.

7. A mild form of acidosis was found in about 30 per cent of the 34 patients.

8. Feces from 19 out of 23 patients showed carbohydrate fermentation, while only 4 showed protein putrefaction. The enzymes were excellent in all cases for amylase, were good in all cases save 4 for protease and were good or fair in all cases for lipase.

9. The metabolic rate seems to be slightly increased in acne vulgaris.

10. The presence of hyperglycemia and the increased basal metabolic rate seem to point toward dysfunction of the thyroid as a possible causative factor. We believe, however, other glands also are at fault.

11. The following measures have proved valuable in the treatment of this condition: Reduction of the carbohydrates in the diet, gastro-intestinal supervision, administration of alkalies and organotherapy.

12. Thyroid in some cases caused the appearance of increased sympathicotonus and increased the severity of the cutaneous condition; occasionally it seemed to produce involution of the lesions.

13. The administration of ovary, lutein and pituitary has been of benefit in some cases.



## THE CLINICAL IMPORTANCE OF ASEPTIC INFARCTION OF THE KIDNEY.

By PAUL W. ASCHNER, M.D.

NEW YORK.

(From the Surgical Service of Dr. Beer, Mount Sinai Hospital, New York City.)

INFARCTION of the kidney is a condition more familiar to the pathologist than to the clinician, as the paucity of clinical literature on the subject attests. That knowledge of its manifestations concerns the surgeon was first impressed upon me when I saw two patients suffering with the condition within a period of two months. Both were admitted to the surgical service as cases in urgent need of operation. Schmidt, in his admirable report of three cases from Neusser's clinic, contrasts the frequency of renal infarcts found at autopsy with the rarity of their clinical recognition. He says that the diagnosis is important for differentiation from conditions requiring early surgical intervention.

The following histories of the cases which were encountered illustrate the practical importance of considering the diagnosis of renal infarction in patients with valvular disease who present the symptoms of an acute intra-abdominal disorder.

CASE I.—M. Z., male, aged thirty-one years, was admitted to the surgical service on the evening of February 16, 1921, with the following history: Two weeks previous to admission he was suddenly seized with sharp pain in the right lower quadrant of the abdomen. The pain lasted about three hours and disappeared spontaneously. It did not radiate nor was it accompanied by vomiting. Two days later he was seized again with severe abdominal pain, cramplike in character, associated with nausea and vomiting. During the following week he had discomfort in the right lower quadrant of the abdomen, with some temperature, and was confined to bed. Three days ago he left his bed, was seized with violent pain in the left flank and vomited. The pain has been present in this location since the onset. It has been constant in character but intensified by bodily motion and deep breathing. The pain on the day of admission radiated downward to the left testicle. For the past week he has had frequency of urination, voiding about every hour. No dysuria, hematuria, nor pyuria.

Examination soon after admission showed a well-developed, well-nourished man, acutely ill, and apparently in severe pain. Pupils and reflexes were normal, the tongue dry and coated, the breath foul. There was distinct voluntary limitation of respiratory excursions. There were dulness and diminished breathing at the

left base posteriorly, but the lower border of the lung came down with deep inspiration. The heart was somewhat enlarged, the apex-beat was in the fifth space 12 cm. from the midsternal line, where a distinct presystolic thrill was felt. A well-marked rumbling presystolic murmur was heard at the apex and transmitted for a short distance into the axilla. The second pulmonic sound was accentuated. The pulse was 90, regular and of good quality. The abdomen was rigid, specially on the left side. There was tenderness over the left lower ribs in the axilla and in the left hypochondrium below the costal border. There was tenderness in the left costovertebral angle also. The left lumbar muscles were rigid. Rectal examination was negative. Temperature, 101.8°F. Blood count: Leukocytes, 20,000; polymorphonuclears, 82 per cent. Urine on admission: Clear; specific gravity, 1020; albumin present; no sugar. Microscopic examination: A few hyaline casts and occasional leukocytes; no erythrocytes.

The differential diagnosis lay between perinephric abscess, subphrenic abscess, infarction of the spleen and infarction of the left kidney. Because of the repeated attacks of pain, first on the right and then on the left side, and the presence of a definite mitral stenosis and of albuminuria, a diagnosis of renal infarction was made. It was therefore decided not to operate immediately.

Under observation the anterior tenderness and muscular rigidity subsided almost completely. The costovertebral tenderness and lumbar rigidity became predominant. The temperature on the day after admission rose to 103°F. Roentgen-ray examination showed no calculus in any part of the urinary tract. Cystoscopy on February 19 showed no abnormality of bladder or ureteral orifices and no obstruction to ureteral catheters. The indigo-carmin appeared in good concentration in twenty minutes on the left side and in somewhat less concentration on the right side in about the same time. Specimens collected for bacteriology proved sterile. Both specimens showed many granular casts and scattered red blood cells (possibly traumatic in origin). The Wassermann test was negative and the blood culture taken on February 17 showed no growth.

February 19, it was decided to explore the left kidney because of the temperature (102°F.) and the persistent and localized tenderness in the left costovertebral angle. The operation performed by the house surgeon, Dr. Jones, revealed a somewhat enlarged kidney with no gross perinephric changes. The kidney was delivered into the wound easily. It presented at its middle and near the lower pole two grayish-white, pearly, circumscribed areas, about 3 cm. in diameter, firm in consistency with surface slightly above the level of the surrounding parenchyma and a narrow injected zone about each of them. Specimens were removed from these areas for pathologic examination. The kidney was

decapsulated and the wound closed with a small rubber-dam drain behind the kidney.

On the day following the operation the temperature rose to 103.2°F. and then gradually returned to normal by lysis, reaching 99°F. by the rectum on the sixth day. All pain and tenderness disappeared. The urine on the day following the operation showed gross blood, and on the sixteenth day after operation still showed a few scattered erythrocytes. The phthalein test on February 24 showed 15 per cent excretion in two hours, and the blood chemistry on February 22 showed urea nitrogen 37.8, incoagulable nitrogen 77, uric acid 2.6, creatinin 1.4. The tissue removed at operation proved to be part of an anemic infarct of the kidney. No microorganisms were found in the stained sections.

The wound healed kindly and the patient was discharged free of all symptoms on March 7, 1921, and has remained well up to the present time. Diagnosis on discharge was mitral stenosis and anemic infarcts of the left kidney.

CASE II.—J. K., female, married, aged forty-four years, was admitted to the surgical service on the afternoon of April 6, 1921, with the following history: About two hours after eating a light lunch on the day before admission she was suddenly seized with severe abdominal cramps. Toward evening the pain localized in the right upper quadrant of the abdomen, where it became constant and intense, occasionally radiating to the back and shoulders. One-half hour after the onset she vomited. The pain was increased by bodily motion, straining at stool and deep breathing. The bowels moved twice with saline catharsis. The patient had been feverish since the onset. There was no history of previous similar attacks and no urinary symptoms. The patient stated that when nine years old she had chorea which was followed by heart trouble. Since that time she had suffered with palpitation and dyspnea on moderate exertion. About one year ago she had an attack of unconsciousness and aphasia lasting several days, but this cleared up completely. She had several abdominal operations for gynecologic conditions.

Examination showed an obese female acutely ill, cyanosed and dyspneic. She was apparently in severe pain. The pulse was rapid, 120 to 130, and very irregular. The temperature was 102.2°F. The abdomen was moderately distended, but soft, except in the right upper quadrant, where there was a moderate amount of rigidity of the rectus. Marked tenderness was elicited in the right hypochondrium and in the midepigastrium, and slight tenderness in the right costovertebral angle. There was hyperalgesia of the skin in the distribution of the 11th, 12th thoracic and 1st lumbar nerves of the right side. The right lumbar muscles were

rigid. The lungs showed no detectable abnormality. The heart was enlarged toward the axilla, the apex-beat being in the 6th space in the anterior axillary line. Cardiac action was absolutely irregular, but no murmurs could be detected. The pulmonic second sound was accentuated. Blood examination: Leukocytes, 24,000; polymorphonuclears, 91 per cent. Urine: Clear; specific gravity, 1018; large amount of albumin; no sugar. Microscopic examination showed many erythrocytes and but few hyaline and granular casts.

The differential diagnosis lay between acute cholecystitis with possible pancreatitis, acute appendicitis, intestinal obstruction due to postoperative adhesions and infarction of the right kidney. The presence of a cardiac lesion and the urinary findings strongly pointed to the last diagnosis. It was therefore decided to postpone surgical interference.

On the following day the tenderness in the right hypochondrium almost completely disappeared, while that in the costovertebral angle became exquisite. Both conjunctivæ showed a few small recent petechiæ, one in the left conjunctiva showing a prominent pearly central spot. On April 8 all anterior tenderness had disappeared, the posterior tenderness persisting. The phthalein test on April 10 showed 35 per cent excretion in two hours. Blood chemistry on April 7 showed: Urea nitrogen, 33.6; incoagulable nitrogen, 59.5; uric acid, 3.8; creatinin, 1.9; cholesterin, 0.18 per cent. Blood Wassermann was negative. Blood culture taken on April 6 was negative.

With the subsidence of acute pain the temperature gradually fell by lysis, reaching 99.2°F. on the seventh day after admission. The urine continued to show large amounts of albumin, casts and a few erythrocytes until April 18, 1921, when merely a trace of albumin was present and a few leukocytes formed the only abnormal elements. On April 12 the patient was transferred to the medical service of Dr. Libman, who concurred in the diagnosis. On April 13 the blood-pressure was systolic 160 and diastolic 80. The leukocytes were 10,200 with 74 per cent polymorphonuclears. Cystoscopy on April 14 showed no abnormality of the bladder or the ureteral orifices. Good indigo-carmin excretion appeared on both sides in eighteen minutes. Specimens collected for bacteriology showed no growth. During the period of observation of seven weeks on the medical service there was no rise in temperature and no further embolic phenomena. The cardiac irregularity persisted in spite of therapy. The electrocardiogram confirmed the clinical finding of auricular fibrillation. The patient was discharged in fair general health with no urinary abnormality except for a faint trace of albumin. Diagnosis: Mitral stenosis and insufficiency, auricular fibrillation and infarction of the right kidney.

It will be noted that these cases have certain features in common. Both patients had mitral valvular disease. The onset in each case was sudden, with abdominal cramps, nausea and vomiting. The pain, then localized to the hypochondriac region, became constant, but was intensified by bodily motion and deep breathing. Tenderness and muscular rigidity predominated anteriorly at first, and later, as the attack subsided, became localized to the lumbar region posteriorly. Albuminuria, cylindruria and erythrocyturia (in one) were present without signs of cardiac decompensation nor the usual manifestations of nephritis. In the absence of pyuria the fever and the marked polymorphonuclear leukocytosis added to the difficulties of diagnosis.

Welch, referring to the question of fever in aseptic embolism, says, "I am not aware of any conclusive observations which show that fever may be produced in this way in human beings." He includes fever, nevertheless, among the general symptoms of renal infarction. Robert Sprinz, in his Inaugural Dissertation at Wurzburg, in 1885, concludes that embolism can produce fever regardless of the nature of the embolized material, and that the fever is due to the embolism, not to the absorption of necrotic tissue from the infarct. Bock has shown experimentally that fever can be produced by the injection into the blood stream of sterile, chemically indifferent particles. Billroth made similar experiments in connection with his studies on wound fever.

Slight fever is noted by Schmidt and Halperin and more marked febrile movement by Riebold. Both Halperin and Riebold report a leukocytosis of over 20,000. The cases here reported show definite febrile movement and well-marked leukocytosis, with all evidence pointing to a bland aseptic infarction.

Senator states that urinary changes occur only with very large or numerous small infarcts and that the presence of blood is essential. Welch, however, says the amount of blood is usually only moderate or even microscopic, and may be absent; hematuria being less common than albuminuria. Chedevergne emphasizes the latter statement in his Paris thèse, 1901, "*De l'albuminurie symptomatique de l'infarction rénal.*"

Schmidt finds albuminuria constant though transient and erythrocyturia uncommon. In complete unilateral infarction the urine may be altogether negative. The absence of formed elements in some cases may be explained by their retention in the infarcted areas. He emphasizes intense oliguria or anuria in bilateral infarction.

The following abstracts are those of cases reported in the literature, grouped according to etiology.

#### A. Cases of thrombosis of the renal arteries.

##### 1. Due to trauma.

Von Recklinghausen, 1861.

Boy, aged eight years, died eight days after a fall. Autopsy revealed severe internal injuries. Circular injury to the coat of the left renal artery two lines in length and one in width;  $\frac{1}{2}$  cm. below this was a large red thrombus; all branches were thrombosed. The kidney was entirely necrotic.

2. Due to infectious diseases (acute arteritis?).

Juhel Renoy.

A girl, aged sixteen years, recovering from scarlatina. Pain in both lumbar regions on the second day of normal temperature, not severe. Complete anuria for six days; death was preceded by several convulsions.

*Autopsy.* No cardiac or aortic lesions. Both kidneys were entirely necrosed. Multiple thrombi in the renal arteries and glomerular tufts. Bacteriologic examination negative.

3. Due to subacute and chronic diseases (arteritis, periarteritis).

Halperin, 1908.

In 1905, a man aged forty-two years, was admitted to Michael Reese Hospital, Chicago. One year ago he had pain in the left big toe after exposure to cold. Five weeks ago the pain recurred and the foot and the lower leg became livid. Gangrene set in and progressed upward. The heart was negative and the urine was normal. Three weeks after admission, fever, sweats, rigors and cough appeared with ascending thrombo-phlebitis of the leg and areas of dulness in the lungs. Urine now showed albumin and casts but no blood. Amputation resulted in recovery.

July 2, 1907. Two weeks' history of pain in the left upper quadrant, vomiting and pain in the left calf. While in the hospital he had two severe attacks of lumbar pain, accompanied by vomiting, headache, fever and leukocytosis of 28,000. Urine: Marked trace of albumin; hyaline, granular and cellular casts, few red blood cells and some hemoglobin. Tenderness in both flanks.

October 6. Severe stabbing pain in the left lumbar region radiating forward to the median line, profuse vomiting and severe headache. The left kidney region was tender. The peripheral vessels were sclerosed. The pain gradually subsided but the urine was suppressed.

October 7. One dram of urine showed much albumin, many pus cells, but no casts or red cells.

October 8. Blood-pressure, 210; temperature, 101°F. Signs of cardiac insufficiency.

October 9. Nine drams of urine obtained showed pus, albumin and hemoglobin. Leukocytes, 16,500; temperature, 99°F. Left kidney explored by Dr. John B. Murphy and found dry, pale gray, practically bloodless.

October 11. Died after six days of almost complete anuria.

*Autopsy.* Left kidney of normal size showed many cicatricial depressions. In midzone a whitish gray infarct,  $7\frac{1}{2}$  cm. in length extending from the cortex to the pelvis and occupying two-thirds of the kidney. The renal artery wall was thickened with a red thrombus at the bifurcation. The right kidney was very small and irregular. There was a large gray infarct of the upper third. There were small cortical infarcts. The renal artery was more thickened than the left, with definite contraction (1 mm. lumen) vessels and branches plugged with adherent red and white thrombi.

*Comment.* Nationality of patient not given. Microscopic studies of vessels not reported. History suggests thrombo-angiitis obliterans.

Pic and Bonnamour, 1913.

Female, aged sixty-nine years, was admitted February 17 to the Hotel Dieu, Paris, for paralysis of the left face and arm. She presented signs of aortic insufficiency, marked arrhythmia and atherosclerosis. The urine was small in amount and decreasing; there was much albumin.

February 24. Temperature rose to  $39^{\circ}$  C., when sudden pain in the left flank and abdomen set in.

February 28. Exitus after progressive alleviation of pain.

*Autopsy.* Dilated atheromatous aorta. Left renal artery and branches completely occluded by a thrombus. Kidney completely infarcted. Pathologist attributed thrombosis to disease of the renal artery and not to embolism.

Manges and Bæhr, 1921.

Man, aged thirty-nine years, was admitted to the surgical service of Dr. Beer, Mt. Sinai Hospital, New York City, June 6, 1919, apparently suffering from some acute abdominal condition. There was a history of cramp-like pains in the calf of both legs radiating to the feet. As these subsided he experienced severe pain in the right lumbar region radiating into the testis, and a few days later had a similar pain on the left side accompanied by hematuria. Six days before admission he had severe epigastric pain, abdominal distention and fever of  $102^{\circ}$ F. Cystoscopy and the roentgen-ray were negative. Leukocytes, 36,000; polynuclears, 75 per cent. After four days the temperature dropped to normal but leukocytosis persisted. Blood-pressure, 160/90. Blood chemistry: Urea nitrogen, 35; incoagulable nitrogen, 95. Urine negative except for a few red blood cells. P. S. P., 64 per cent.

June 19. Exploration by Dr. Buerger for suspected retroperitoneal abscess revealed periarteritic nodules on the mesenteric vessels. He was then transferred to the medical service, where he developed nodules on the peripheral vessels. In the course of four months he developed signs of progressive renal insufficiency and died of a terminal bronchopneumonia.

Autopsy showed extensive periarteritis nodosa involving many of the small and medium-sized arteries. The most extensive lesions were found in the kidneys. The right kidney showed dense perinephritis, a false aneurysm in the cortex, occlusion of nearly all the renal arterial branches by thrombi. The left kidney was small, its surface studded with large depressed scars the result of numerous old infarctions, and its vessels extensively diseased. The cortical markings were completely obscured in both organs.

B. Cases of embolism of the renal arteries:

Traube, 1853.

Machinist, aged eighteen years, with aortic insufficiency.

October 14. At 1 A.M., sudden onset with pain, awoke from sleep. Pain intensified by pressure over the right kidney, by bodily motions and cough; lessened by lying on the right side and by leeching. It radiated into the right thigh. The urine before the attack was small in amount dark and sedimented. After the attack it was diminished in amount and was dark, with uric acid sediment but no albuminuria. Pressure sensation in the bladder region, dysuria, increased pulse-rate and restlessness.

October 19. Vomiting and collapse, fear and restlessness and air hunger. Died nine days after onset.

*Autopsy.* The aortic valves were incompetent, with warty vegetations. Splenic infarct the size of a hazelnut. Old small infarcts of both kidneys, but the right showed a large infarct extending from the convex border to the pelvis, two inches long and prominent.

Bartels, 1870.

Boy, aged eight years, previously tracheotomized for croup, suddenly developed pain in the region of the spleen, which became enlarged. Several days later pain in the left thigh, followed by paresis of the extremity and death in four days. There were no urinary symptoms.

*Autopsy.* Large splenic infarct. Large left renal infarct; renal capsule and perirenal fat thick and swollen. The renal artery and its branches were thrombosed. Healing lesions of diphtheria. Thrombus in the apex of the left ventricle, with ragged, broken surface (probable source of emboli).

Von Leube, 1895.

Cabinet-maker, aged seventeen years. Acute endocarditis (aortic insufficiency) in the course of acute articular rheumatism. The patient's urine contained albumin and blood. The left kidney region was very tender. No edema. Blood disappeared in two days and the albumin in six days. On March 6, pressure in the chest, headache, and fever of 38.6° C. appeared. The urine again showed



albumin and blood and the left kidney again became tender. Urinary changes persisted seven days, then all the symptoms subsided. Diagnosis of renal infarction was made. The patient recovered.

Chedevergne, 1902.

Male, aged twenty-two years, with aortic and mitral disease. Urine negative over long periods of observation in two hospitals. Returned six days after discharge with marked dyspnea and arrhythmia but without passive congestion. Urine now showed a large amount of albumin without casts. Sudden pain in the popliteal space of the right leg. Urine decreased in amount without increased concentration; the albuminuria increased. Gangrene of the right leg at first dry, then moist supervened, and death ensued with septic phenomena.

*Autopsy.* Mitral stenosis and secondary insufficiency of the aortic and tricuspid. Kidneys showed several deep depressions. The left kidney showed a recent infarct the size of an olive. The right femoral artery was occluded.

Schmidt, 1901.

Laborer, aged forty years; had rheumatism, pleuritis and carditis four years ago.

September 25. The patient was admitted with dyspnea, cyanosis and venous engorgement of the lungs and the liver.

October 10. Sudden pain in the right flank, increasingly intense.

October 11. Tender in the right lumbar region posteriorly and under the liver anteriorly; vomiting, hiccough, constipation.

October 13. Pain was aggravated by motion, breathing, vomiting, etc., and was relieved by lying on the affected side.

October 14. Pain disappeared but the lumbar tenderness persisted.

October 17. Peritoneal friction rub was felt anteriorly below the liver. The urine was not diminished; no changes. No fever. Sudden exitus the next day.

*Autopsy.* Healed endocarditis of the mitral valve. Extensive anemic infarct of the right kidney with hemorrhage into the renal capsule.

Schmidt.

Female, aged twenty-one years, had recurrent polyarthritis with cardiac involvement. Two years ago had hemiparesis, which gradually cleared up.

December 16, 1899. Admitted, complaining of anorexia, attacks of dizziness, headache and precordial pain. Findings, delicate individual, with slight flush and cyanosis. Mitral stenosis and insufficiency. Urine: 1022; amount, 1000 cc. Nucleo-albumin + serum-albumin—No fever.

February 26, 1900. Discharged improved.

November 6, 1900. Readmitted, with slight edema of the legs.

December 2. Severe pain in the gall-bladder region, radiating to the lower thorax and flank; incessant vomiting and marked dyspnea; tenderness in the right flank.

December 3. Similar attack on the left side. Pain was relieved by lying on the belly, but was increased by deep breathing and movement of the right hip.

December 4. Almost complete suppression; hiccough; constipation; comfortable only with knees flexed.

December 6. Retention and oliguria; obstipation; headache; hiccough.

December 7 to 9. Retention and oliguria persist. Gastro-intestinal disturbance continued.

December 16. Progressive loss of weight and strength.

December 21. Exitus.

Highest temperature was 39° C. (December 4). There was one chill.

(December 5). Urine was entirely negative before the attacks. After the attacks there was marked oliguria and albuminuria, with red blood cells. No casts or renal elements.

*Autopsy.* Healed mitral lesion with lime deposit. Numerous infarcts of the kidneys, specially the left. Numerous large infarcts of the spleen.

Schmidt.

Man, aged forty-five years, with mitral stenosis and insufficiency, who had responded to digitalis in several periods of decompensation.

December 6, 1901. Sudden attack of pain in the right upper abdomen with vomiting, dizziness and collapse. Pain localized to the right kidney region a few hours later.

December 7. Similar pain but less severe in the left kidney region. The pain was deep seated, constant and made worse by bodily motion and deep breathing. Tender to percussion over both kidneys and to pressure anteriorly below the costal border. Anorexia, vomiting and constipation, which persisted four days. Ileocecal region was tender. Great difficulty in voiding.

December 10. Leukocytes, 11,000. Temperature, 38.3°C.

December 16. Apparently well.

December 17. Epileptiform seizures followed by coma. Signs of right hemiplegia. Pulse in the left radial and brachial regions disappeared. Exitus.

Urinary changes were of interest. Oliguria with onset of renal infarction. Postembolic polyuria hitherto unobserved was noted. Only a few red cells were in the sediment. Definite albuminuria.

Epithelial casts of polygonal cells with red cells attached to each cast were found.

December 6, 7, 8. Casts of brownish color covered with urate, waxy-like casts and a few free red blood cells.

*Autopsy.* Old double mitral lesion, thrombus in the left auricle, multiple anemic infarcts of both kidneys. Infarcts of spleen. Embolus in the left Sylvian and left brachial arteries. Erosions of gastric mucosa.

Riebold, 1905.

Housemaid, aged twenty-nine years, suffering with cardiac decompensation and irregularity, the result of rheumatism seven years previously. Mitral stenosis and insufficiency. Improved under digitalis.

October 11. Sudden severe pain in the left flank, with nausea, vomiting and collapse. Pain constant, localized, aggravated by bodily motion and deep breathing. Abdomen distended, tender, specially in the left upper quadrant, with marked skin hyperalgesia. Marked constipation, no passage of gas. Temperature, 37.6° C.

October 12. Continued vomiting and pain. Spleen enlarged. Retention, but catheter yielded 500 cc of normal urine. Leukocytes, 21,600; temperature, 38.9° C.

October 13. Less pain, no vomiting, but obstipation with tenderness in the left upper quadrant.

October 14. Bowels moved and urine voided, but severe pain reappeared in the left flank and also appeared in the right flank.

October 16. Sudden right hemiparesis.

October 17. Exitus.

*Autopsy.* Left kidney; upper half completely infarcted, multiple small infarcts in the lower half. Perirenal tissue thick and edematous. Embolus lodged in the renal artery. Right kidney: Two cherry-sized fresh infarcts. Spleen: Wedge-shaped anemic infarct, the surface of which showed fibrinous exudate. Embolism of the basilar artery. Double mitral lesion.

Von Jagic, 1915.

Female, aged thirty-nine years, with post-rheumatic cardiac disease; two weeks prior to admission, February 10, 1914, had an attack of pain in the left side of the abdomen, cramp-like and persistent. She presented signs of mitral and tricuspid disease, marked abdominal distention, with tenderness in the left lower quadrant, but no rigidity or rebound sign. Evening temperature, 39.2° C. Urine: 500 cc; specific gravity, 1023; much albumin, no blood. After three or four days there was a subsidence of pain and temperature.

February 14. Sudden rise in temperature to 38° C.

February 16. Repeated vomiting and severe pain on the right side, and a tender mass below the costal border.

February 27. Sudden exitus.

*Autopsy.* Mitral and tricuspid stenosis. Thrombi in the left auricle and ventricle. Emboli in both renal arteries, with anemic infarction of large areas of parenchyma.

### C. Cases of doubtful etiology.

Gayet and Favre, 1914.

Female, aged thirty-four years, had typhoid with albuminuria in 1904. Vague renal pain simulating stone colic appeared in 1908. In 1913, urinary symptoms and attacks of colic led to cystoscopy. The right kidney function was half that of the left, some pus and colon bacilli. Roentgen ray was negative.

January, 1914. *Operation.* Right nephrectomy. Kidney showed infarct of half the kidney with small calcific lesion at the center. Was it due to typhoid or was it a sclerocyst about a small calculus?

Rathbun, 1916.

Russian teamster, aged thirty years, noted frequency and urgency of the urine one and a half years ago. One year ago had dull pain in the left flank with radiation along the ureter, growing progressively worse. The left kidney was palpable and tender to pressure and percussion. All examinations were negative. Equal and good excretion of P. S. P. from the kidneys. Congestion of the posterior urethra was relieved by treatment, but lumbar pain persisted.

May 5, 1916. *Operation.* Kidney enlarged and showed several hard lumps. Organ split and four lumps of fibroid consistency noted. Kidney had to be removed later for hemorrhage, and lesions were found to be infarcts with plugged vessels and coagulation necrosis. The patient had no cardiac lesion. No abnormality of urine was detected preoperatively.

*Comment.* Note strong resemblance to pseudogummatous lesions described by Beriel and Devic (les sequestres des reins).

**Etiology.** The immediate cause of renal infarction is the shutting off of the blood supply to smaller or larger areas of parenchyma. This may be due to thrombosis in the renal artery or its branches brought about by trauma, acute arteritis in the course of an infectious disease, chronic arteritis, atherosclerosis or periarteritis nodosa. Embolism is a more common cause of infarction. Chronic valvular disease was the cause of embolism in 10 cases, of which 2 were aortic and 8 mitral. The mitral lesions were stenotic and in 2 thrombi were found in the left auricle. The problem of embolic phenomena in valvular disease has been studied by Libman in connection with subacute bacterial endocarditis in the healing

or healed stage. In his opinion valvular defects *per se* do not provide emboli which produce clinically recognizable phenomena. When such phenomena do occur in patients with chronic valvular disease and bacteria-free blood the presumption is strong that the rheumatic infection has been followed by a bacterial invasion which has gone on to spontaneous healing.

It is important to remember that while infarcts occurring in the active bacterial stage of the disease do not suppurate, nevertheless the emboli producing these lesions are not aseptic.\*

Aseptic emboli may come from thrombi in the pulmonary veins or the left auricle; from atheromatous lesions, ulcers, fibrinous deposits, thrombi or calcified vegetations on the mitral and aortic valves, or from atheromatous lesions of the aorta. Paradoxical emboli passing from some peripheral vein through an open foramen ovale or open septum may produce infarction.

Such conditions as aneurysm of the renal artery, thrombosis of the renal veins and infarction of the renal cortex in eclampsia do not come within the scope of this paper, as their clinical manifestations are different.

**Onset.** In the cases associated with chronic valvular disease the onset is sudden with severe pain in the abdomen and flank accompanied by vomiting, fever and more or less prostration and signs of collapse. In a few cases there was a history of mild indefinite attacks on the same or opposite side.

**Pain.** The first symptom is sudden, severe pain referred to either hypochondrium below the costal border or even to the lower quadrants of the abdomen. It is maximum at onset, constant not colicky, and variously described as cutting, pressing or burning. Morphine is required for its relief. It is intensified by deep breathing, coughing, retching, straining at stool, by bodily motions and extending the thighs. It is lessened by lying on the affected side and flexing the thighs. In a bilateral case the patient may lie on the belly to obtain relief.

As the pain diminishes, in the course of twenty-four hours, it tends to localize to the lumbar region posteriorly. In some cases the pain is referred to the back and flank from the outset. Radiation to the thigh and to the testicle occurred twice.

Tenderness and muscular rigidity are chiefly anterior at first and strongly suggest some acute intraperitoneal disorder. Lumbar percussion, however, causes pain from the beginning. As the acute pain of onset subsides the anterior tenderness and rigidity diminish, costovertebral tenderness and lumbar rigidity become predominant.

According to Schmidt the pain is due to three factors: Increased intracapsular pressure, damage to the renal plexus along the vessels

\* Jurgensen's case, Nothnagel's Handbuch, 15, 105, has been excluded because it probably belongs in this category.

and perinephritis. Localization depends on the position of the kidney and the nerve trunks affected. Thus the areas of skin hyperalgesia correspond to the 11th and 12th thoracic and 1st lumbar nerves, and pain may occur in the distribution of the iliohypogastric nerve. Perinephric hemorrhage, edema or thickening are noted in four autopsies.

**Associated Vascular Phenomena.** In 2 cases there was a history of cerebral embolism producing aphasia in one and hemiparesis in the other, both having completely cleared up. One of my cases had conjunctival petechiae. Splenic infarcts occurred in 5 cases. Embolism of the femoral, brachial, Sylvian and basilar arteries with their resultant disturbances were also noted in the course of the disease. In the case of chronic endarteritis of the renal vessels (Halperin's case) there was a preceding gangrene of the leg due to disease of the vessels. The case of periarteritis nodosa naturally presented widespread vascular lesions and their effects.

**Fever and Leukocytosis.** These have been discussed in preceding paragraphs.

**Urinary Symptoms and Changes.** Bladder function was disturbed in 5 cases; in 1 there was frequency and urgency, in 1 dysuria, in 1 there was great difficulty in voiding, and in 2 there was actual retention. In 3 cases no urinary changes were observed. Marked diminution of urine was noted in 5 cases and complete or almost complete suppression occurred in 2. Albuminuria was present in 9 cases to a marked degree and constituted the most frequent urinary abnormality. Macroscopic hematuria occurred only in the case of periarteritis nodosa, and contrary to the usual belief was not a part of the clinical picture. Erythrocytes were present in 6 cases, and in 6 their absence was specifically recorded. Casts, hyaline, granular or cellular, were present in only 4 cases.

**Gastro-intestinal Symptoms** are prominent in the clinical picture. Nausea and vomiting at the onset, often persistent and incessant, abdominal distention, constipation or even obstipation, together with the referred pain, tenderness, rigidity of the abdominal muscles, fever and leukocytosis strongly incline one to suspect some acute intraperitoneal disorder requiring immediate surgical intervention. These symptoms are of reflex origin at first and toxic or suburemic afterward.

**Diagnosis.** To establish a clinical diagnosis of aseptic renal infarction we must find a source for an aseptic embolus (usually valvular disease) or evidence of some constitutional or vascular disease which can produce thrombosis in the renal vessels. In cases of valvular disease we must exclude active bacterial forms of endocarditis. Of the symptomatology emphasis should be placed upon the sudden onset with abdominal pain and gastro-intestinal disturbances. It is characteristic for the pain to be anterior at first and to localize to the kidney region later. Lumbar

percussion, however, elicits pain from the beginning and costovertebral tenderness persists after spontaneous pain has ceased. While urinary abnormalities are not constant the presence of albumin and erythrocytes is confirmatory.

**Differential Diagnosis.** The conditions with which renal infarction may be confused have been indicated in part. The most important is that group of intraperitoneal disorders which requires surgical intervention, namely: Appendicitis, cholecystitis, intestinal obstruction, mesenteric vascular occlusion, perforative peritonitis. A second group of cases is that resulting from obstructive lesions in the ureter occasioned by the presence of or passage of a calculus, blood-clots, inflammatory, leukoplakic or tumor tissue, or by angulation, spasm or inflammatory swelling of the ureter. A third group of cases is that in which renal pain results from sudden increase of intracapsular pressure without obstruction in the urinary passages. Such would be produced by torsion of the vascular pedicle of a floating kidney, compression of the renal veins by retroperitoneal hematomas or inflammatory processes, hemorrhage or congestion in a renal neoplasm. Exacerbations in chronic inflammations of the kidney, as in so-called nephralgie hematurique, produce a similar condition and are specially difficult to differentiate. The renal congestional colics occurring in connection with menstruation as described by French authors also belong in this group.

Schmidt gives a very complete discussion of the details of differentiation.

**Prognosis.** Of the cases collected, Leube's and my own recovered. The 2 cases of doubtful etiology and pathology recovered after nephrectomy. Bilateral renal infarction occurred in 7 cases, in 5 of which marked suppression or anuria resulted in death. Other embolic lesions appeared to have caused death in 4 cases. In 1 unilateral case the cause of death is not clear; in 1 suppression occurred. Although a patient may recover completely from an attack of renal infarction the underlying disease places him in constant danger of subsequent attacks and of other more serious embolic or thrombotic accidents.

#### BIBLIOGRAPHY.

1. Bartels: Untersuchungen über die Embolische Prozesse von Dr. J. Cohnheim, 1872, p. 77.
2. Beriel and Devic: Lyon méd., 1913, 120, 1263.
3. Billroth: Arch. f. klin. Chir., 1872, 13, 579.
4. Bock: Arch. f. exper. Path. u. Pharmacol., 68.
5. Chedevergne: Paris Thèses, 1901-2, No. 375.
6. Gayet and Favre: Lyon méd., 1914, 122, 349.
7. Halperin: Arch. Int. Med., 1908, 1, 320.
8. von Jagie: Wien. med. Wchnschr., 1915, 65, 290.
9. Juhel Renoy: Traité de médecine (Charcot, Bouchard et Brissaud), 5, 643.
10. von Leube: Spezielle Diagnose der inneren Krankheiten, 1895, p. 341.

11. Libman: AM. JOUR. MED. SC., 1913, 146, 625. Med. Clin. of North America, 1917, 1, 573.
12. Manges and Baehr: AM. JOUR. MED. SC., 1921, 152, 182.
13. Pic and Bonnamour: Lyon m  d., 1913, 120, 1306.
14. Rathbun: New York Med. Jour., 1916, 104, 734.
15. von Recklinghausen: Virchow's Arch. f. path. Anat., 1861, 20, 205.
16. Ricbold: Deutsch Arch. f. klin. Med., 1905, 84, 498.
17. Schmidt: Wien. klin. Wchnschr., 1901, 14, 451 and 486; 1902, 15, 643.
18. Senator: Die Erkrankungen der Nieren, p. 131.
19. Sprinz: Inaugural Dissertation, Wurzburg, 1885.
20. Traube: Ueber den Zusammenhang von Herz und Nierenkrankheiten, 1856, p. 77.
21. Welch: Allbutt and Rolleston's System, 6, 742, 762, 803.

## THE STUDY OF VESTIBULAR NERVE FUNCTION IN MYXEDEMA.\*

By ROY A. BARLOW, M.D.

SECTION ON OTOLARYNGOLOGY AND RHINOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA.

THE study of the phenomenon of lowered irritability was suggested by the occasional finding of nerve deafness in certain myxedematous patients. As we know, myxedema, or hypothyroidism, is a condition arising from dysfunction of the thyroid gland and manifesting itself by change in weight, cardiac disturbances, dry skin, and other visceral upsets, associated with a certain slowness in response to external stimuli.

From time to time additional data have been added to our knowledge of the interesting condition of myxedema. In recent years light has been thrown on the clinical picture of the condition by the work of Plummer, and Boothby and Sandiford, along the lines of the basal metabolic rate. This work, in conjunction with the isolation of the active principle of the thyroid gland by Kendall, has been of inestimable value in the manipulation of such cases. The literature on the subject has been well combed and brought to date by Lissner, who discusses at length the various changes in the special senses in cretins and in myxedematous patients. St. Lager has reported 5000 cretins in Switzerland and 4000 deaf mutes; 80 per cent of the latter were cretins. Scholz found that 29 per cent of cretins were deaf mutes and that 32 per cent of the others were hard of hearing. Hammerschlag, who was one of the first carefully to investigate the condition, found peripheral ear changes and disturbances in the bone conduction. Various theories and hypotheses have been advanced with regard to the changes taking place, such as ossification of the stapes, impaired development of the epithelial cells in the ductus cochlearis, and so forth. In cases in which the thyroid gland has developed a dysfunction after

\* Thesis submitted for membership in the American Laryngological, Otological and Rhinological Society, 1921.



puberty, marked disturbances of hearing are found which can readily be distinguished from the endemic variety by the rapid and spectacular improvement following thyroid therapy.

Lisser calls attention to the fact that Wagner supposed the impairment in hearing was due to myxedematous swelling of the mucous membrane of the middle ear, but Denker found that in thyroidectomized dogs, that had become entirely deaf after operation, there were no histologic changes of a myxedematous character, and stated that the question remained unsettled. It was this statement that prompted me to investigate, clinically, the eighth nerve tracts by equilibration tests.

The literature on the subject of myxedema, which is most voluminous, constantly directs attention to the fact that such patients complain of deafness and tinnitus, but nowhere in the available literature have I been able to find a single reference based on the function of the eighth nerve tracts as demonstrated by the Bárány tests. While the results of my investigation may not be of paramount value in themselves, they are nevertheless an additional bit of datum to the sum total of recorded findings.

Fifteen cases of myxedema were studied; these had been definitely diagnosed as such by the clinical findings in conjunction with the various laboratory tests, most noteworthy of which is the determination of the basal metabolic rate. I shall not dwell on the various changes, such as dry skin, lack of perspiration, and so forth, or quote profuse statistical material which in itself is more or less confusing, but shall make a preliminary report on the cases studied thus far. The equilibration test was made at about the same time the basal metabolic rate was taken. Some of the patients were placed on thyroid therapy and have reported their improvement by proxy. Except in one or two instances they have not as yet been tested to note the improvement, if any, in the eighth nerve tracts.

#### SUMMARY OF CASES.

CASE 1 (200923).—Mrs. R. O. L., aged forty-nine years, came for examination, July 14, 1917, complaining of indefinite gastric symptoms and increased weight. The general examination was negative. February 28, 1918, the metabolic rate was taken and found to be  $-17$  per cent.

The hearing test showed a slight nerve involvement such as is seen with edema of the internal ear. The equilibration test showed a definite reduction in irritability, especially on the left side. The reduction was most marked in the reaction time.

CASE 2 (235663).—Miss T. R., aged eighteen years, was examined, June 20, 1918. She had metrorrhagia and appeared anemic. Her

hemoglobin was 65 per cent and her basal metabolic rate, taken June 22, was -32 per cent.

The hearing tests were normal. Equilibration tests showed a slight spontaneous nystagmus and delayed induced nystagmus; the amplitude also was reduced. The pointing response was of doubtful significance. This case shows mainly a reduction in time and amplitude of nystagmus.

CASE 3 (236779).—Mrs. J. H. P., aged sixty-two years, came for consultation, July 5, 1918. In the course of examination it was found that she had a basal metabolic rate of -32 per cent.

The equilibration tests showed that the stimuli went through, but with reduction in time in nystagmus for horizontal tracts and reduction in amplitude for vertical tracts. Hearing tests showed an eighth nerve reduction, hearing nothing in Schwabach's test. She was given thyroxin in 0.25 mg. doses three times a day and August 1, 1918, her basal metabolic rate was +1 per cent. Symptomatically she was greatly improved. A Bárány test was attempted. The hearing had improved. In an attempt to test the tracts with cold water she became violently nauseated and the test could not be continued. She had a decided sensation of falling.

This is the only case in the series in which an opportunity was afforded to check up after treatment. The findings indicate that it may be possible in later studies to demonstrate improvement in the results of the Bárány tests.

CASE 4 (262235).—Mrs. W. A. E., aged forty-nine years, was examined, February 28, 1919. She stated that she had noticed an increase in weight, palor, and puffiness, and a change in voice tone. Her skin was dry and her mentality somewhat retarded. General examination was negative, except that the hemoglobin was 10 per cent, and the basal metabolic rate was -22 per cent.

The hearing test showed some reduction in tone appreciation. The equilibration test showed no spontaneous nystagmus and a reduction in amplitude of induced nystagmus, although time reaction was not disturbed. The pointing reaction was not brought out, although there was a slight spontaneous fault with the left.

CASE 5 (262555).—Mr. F. M., aged thirty-nine years, a farmer, came for examination March 4, 1919, complaining of progressive muscular weakness of four years' duration. His skin was yellowish-white. His muscular movements had become markedly slower and he had difficulty in keeping warm. His basal metabolic rate was -40 per cent and his weight was 142.5 pounds.

The equilibration examination showed that in addition to a lowered bone conduction, there was no spontaneous nystagmus. The nystagmus induced with caloric irrigation showed slight delay

and diminished amplitude in the rotatory nystagmus. There was almost no vertigo. The pointing was not brought out with the head erect in the right horizontal canal, but was well elicited with the head thrown back. The left did not respond on the right when the left canal was stimulated, but was present with the left hand.

CASE 6 (270161).—Mrs. W. S., aged forty-five years, was examined, July 7, 1920. She had had a thyroidectomy and her symptoms pointed to insufficient thyroid function. Her basal metabolic rate was  $-28$  per cent.

The equilibration test was negative. The hearing test was normal. The nystagmus time was prompt and the amplitude well marked. There was no past pointing fault, save a failure to respond on stimulation of the left ear, and past pointing with the right hand with the head erect. Other than this discrepancy, it might be said that this patient showed very slight, if any, disturbance as demonstrated by the Bárány test.

CASE 7 (281940).—Mrs. H. M. A., aged fifty-one years, came for examination, August 1, 1919, complaining of general lethargy and decrease in weight. She noticed that she had difficulty in remembering, that mentally she did not grasp things. Her basal metabolic rate was  $-39$  per cent.

Hearing tests were normal, but equilibration tests showed a slight spontaneous nystagmus on looking to right or left and a delayed time in after-nystagmus, with reduction in vertigo. The induced nystagmus was missing in the verticals even after three minutes' irrigation, although the pointing responses were elicited. The horizontal canals gave fair response with the head thrown back. There was no nausea with stimulation. The cerebelli were in normal response, but the reduction was largely in the midstem.

CASE 8 (284646).—Miss L. W., aged fourteen years, came for examination, August 2, 1919, complaining of loss of appetite and weight, and considerable weakness. Her parents had noticed that she was slow of speech and somewhat mentally dull. The examination of the heart, lungs, and kidneys was negative. Her hemoglobin was 74 per cent and her basal metabolic rate was  $-36$  per cent.

The hearing tests were normal. The equilibration tests showed a spontaneous nystagmus horizontal. On irrigation the nystagmus from the vertical tracts was found to be delayed; the after-nystagmus in the horizontal tracts was prompt on the right but not induced on the left. There was also a decrease in the past pointing response from the left with the head thrown back. Otherwise the past pointing was fairly prompt.

CASE 10 (307493).—Miss G. H., aged twenty-six years, was examined, February 27, 1920. She presented rather an indefinite clinical picture, with gradual onset of abdominal distress and some increased nervous instability. Her basal metabolic rate was  $-22$  per cent; her weight was 119.25 pounds.

The equilibration tests showed practically normal hearing. The patient had a slight spontaneous nystagmus but no pointing fault. Under caloric stimulation she showed a delay in responses but no nausea. The pointing reaction was not materially interfered with except the horizontal canal, and it should be noted that the degree of amplitude in the nystagmus induced was less than with the head thrown back. There was no tendency to falling. Irritability was reduced.

CASE 12 (324843).—Mrs. M. F. T., aged sixty-seven years, came for examination, July 16, 1920, complaining of abdominal distention, constipation, shortness of breath, puffiness under the eyes, and swelling of the extremities. The routine examination revealed a basal metabolic rate of  $-17$  per cent, July 23, and  $-26$  per cent, July 28.

The hearing test was normal and equilibration tests showed no spontaneous disturbance either of nystagmus or pointing. The nystagmus on stimulation was not delayed. There was only slight nausea. The past pointing was elicited well, except on stimulation of the left ear, with the head back, when the left side did not respond, although the right was quite pronounced.

CASE 13 (313335).—Mrs. M. L., aged fifty-seven years, came for examination, April 22, 1920. She had a malignant tumor of the thyroid. Her basal metabolic rate was  $-25$  per cent.

The equilibration test showed slight deafness; no spontaneous nystagmus or pointing fault. On caloric stimulation she was found to have a slight delay in nystagmus time and a slight reduction in past pointing. She was weak and it was doubtful how much the hypothyroidism influenced the tests, or whether the delayed responses might be explained by the patient's weakened condition.

CASE 14 (331963).—Mrs. J. N., aged fifty-three years, was examined, August 30, 1920. The routine tests were made. The basal metabolic rate was  $-26$  per cent.

The hearing test showed only a slight lowering of bone conduction. Equilibration test showed a slight spontaneous nystagmus on looking to the right. On caloric stimulation she was found to have prompt responses of good amplitude. There was good response in the past pointing. Altogether, this case showed very slight changes of indeterminate significance.

## TABULATION OF THE CASE HISTORIES

## CASE 1 (200923)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	-2	-2						
C-1 . . . . .	-5	-5						
C-4 . . . . .	-6	-6						

## Caloric test—68° F.

## Remarks:

Irritability definitely reduced throughout

1	3	↪ 1'40"	↩ 1'40"		
1	2	→	←		

## CASE 2 (235663)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . . .	Normal	Normal						
C-4 . . . . .	Normal	Normal						

## Caloric test—68° F.

## Remarks:

Nystagmus very slight, slowly induced; irritability markedly reduced

Touch	Touch	↪ 1'10"	↩ 1'		
1	2				
1	1				
Touch	Touch	→	←		

## CASE 3. (236779)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Loud whisper	Loud whisper	Touch	Touch	0	0	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	-7	-6						
C-1 . . . . .	-20	-14						
C-4 . . . . .	-15	-10						

Caloric test—68° F.

Remarks:								
Responses retarded	2	2	↷ 2'10"	↶ 1'15"				
	2	2						
	2	Touch	→	←				
	2							
	Touch							

CASE 4 (262235)

Spontaneous responses.

Hearing			Pointing.		Nystagmus.			
	Right.	Left	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . .	-10	-6						
C-4 . . . .	-8	-6						

Caloric test—68° F.

Remarks:								
Time normal; amplitude and responses markedly reduced	Touch	Touch	↷ 1'35"	↶ 1'40"				
	1	1	→	←				

CASE 5 (262555)

Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	..	+						
Rinne's test . .	+	+						
Schwabach's test	-5	-5						
C-1 . . . .	Normal	Normal						
C-4 . . . .	Normal	Normal						

Caloric test—68° F.

Remarks:								
Responses delayed, amplitude small	Touch	Touch	↷ 1'5"	↶ 1'20"				
	Touch	Touch						
	4	6	→	←				
	..	6						
	..	8						

## CASE 6 (270161)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent ?	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . .	Normal	Normal						
C-4 . . . .	Normal	Normal						

## Calorie test—68° F.

## Remarks:

Responses normal, slightly reduced	4	4	↖ 1'	↗ 1'30"
	6	8		
	2	4	→	←
	4			
Touch				

## CASE 7 (281940)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test . .	+	+						
Rinne's test . . .	+	+						
Schwabach's test	-4	-3						
C-1 . . . .	Normal	Normal						
C-4 . . . .	Normal	Normal						

## Caloric test—68° F.

## Remarks:

Rotatory nystagmus not induced	3	2	0 3'	0 3'
	14	4		
Rotatory nystagmus not induced	2	3		
	..	3	→	←
		Touch		

## CASE 8 (284646)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	→	←	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . . .	Normal	Normal						
C-4 . . . . .	Normal	Normal						

## Calorie test—68° F.

## Remarks:

Irritability reduced throughout; no localization

4  
4  
5  
6  
12  
1  
Touch↷ 1'4"  
→↶ 1'30"  
0

## CASE 9 (285377)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . . .	Normal	Normal						
C-4 . . . . .	Normal	Normal						

## Calorie test—68° F.

## Remarks:

No rotatory nystagmus after three minutes, reduced horizontal; responses reduced

1  
1  
2  
13  
1  
Touch  
Touch0 3'  
→0 3'  
←



## CASE 10 (307493)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . . .	Normal	Normal						
C-4 . . . . .	Normal	Normal						

## Caloric test—68° F.

## Remarks:

Responses delayed, irritability reduced; no nausea

2	3	↪ 1'26"	↪ 1'32"
6	4		
2	3		
4	4	→	←

## CASE 11 (308604)

## Spontaneous responses

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	Normal	Normal						
Rinne's test . .	+	+						
Schwabach's test	-2	-2						
C-1 . . . . .	-2	-2						
C-4 . . . . .	-4	-7						

## Caloric test—68° F.

## Remarks:

Responses delayed  
Responses delayed

1	3	↪ 1'25"	↪ 1'40"
3	5		
1	4	→	←
3	5		

## CASE 12 (324843)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	Normal	Normal						
C-1 . . . .	Normal	Normal						
C-4 . . . .	Normal	Normal						

## Caloric test—68° F.

Remarks:								
Time delayed; amplitude small	10	8	→ 1'	← 1'15"				
	10	6						
	10	6	→	←				
	10	Touch						

## CASE 13 (313335)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	..	+						
Rinne's test . .	+	-						
Schwabach's test	Normal	Normal						
C-1 . . . .	Normal	-12						
C-4 . . . .	Normal	-2						

## Caloric test—68° F.

Remarks:								
Responses slightly delayed	2	2	→ 1'10"	← 0'50"				
	3	3						
Responses delayed	..	2	→	←				
	..	3						

## CASE 14 (331963)

## Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up	Down
Noise apparent .	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test . .	Normal	Normal						
Rinne's test . .	+	+						
Schwabach's test	-6	-6						
C-1 . . . . .	Normal	Normal						
C-4 . . . . .	Normal	Normal						

## Caloric test—68° F.

## Remarks:

Responses fine in character, prompt	6	4	↖ 0'45"	↖ 0'35"		
Responses prompt; slight nausea .	4	4	→	←		
	5	4				
	4	4				

## CASE 15 (359522)

## Spontaneous responses

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up	Down.
Noise apparent .	Whisper	Whisper	Touch	Touch	←	0	0	0
Weber's test . .	+	+						
Rinne's test . .	+	+						
Schwabach's test	-2	-2						
C-1 . . . . .	-8	-10						
C-4 . . . . .	-3	-2						

## Caloric test—68° F.

## Remarks:

Responses somewhat slow	Touch	Touch	0 3'	↖ 1'45"		
	9	2				
	2	2	→	←		
	..	2				
	..	3				

On the Bárány sheets it may be noted that retardation in response was demonstrable in 73 per cent of the cases. Cases 1, 2, 7, 8, 9, 10, and 15 show spontaneous nystagmus. Lowered bone conduction\* was noted in Cases 5, 7, and 14 only. "Lowered bone conduction" indicates that bone conduction was demonstrated to be lowered in an otherwise normal hearing test, or lowered out of proportion to the rest of the hearing test. There was no spontaneous pointing fault noted.

The caloric test consisted of irrigating the ear with water at 68° F. The nystagmus produced, if any, was recorded; the past pointing test was then made, the head was thrown back, and the nystagmus, if any was noted; the past pointing test was again made. The most prominent finding was that of a delayed response in time or a reduction in amplitude of nystagmus or past pointing, or a combination of all. The degree of retardation was variable, as, for instance, in Case 15, in which nystagmus was absent when the right ear was irrigated and past pointing fault was not noted with the head erect, as compared with Case 6, in which the nystagmus was prompt on the right and responses fairly normal. Case 7 gave no response to stimulation with the head in an erect position with nystagmus, but nevertheless, the stimulus penetrated sufficiently to produce a past pointing fault, with the exception of the left hand and on stimulation of the right ear. In this case, however, with the head thrown back a prompt response was obtained in the nature of a horizontal nystagmus and a well-marked past pointing response. In Cases 1, 2, 3, 8, 10, 11, and 13 there was a generalized retardation or reduction in response to caloric stimulation. In Cases 2, 4, 5, 12, and 14 a reduction in amplitude of the nystagmus and after-nystagmus was found. In Case 3 the responses were retarded, the past pointing test with the right hand and on stimulation of the left ear was not elicited, and the past pointing tests throughout were somewhat reduced. The patient was placed on thyroid therapy and was found within four weeks to have a basal metabolic rate of +1 per cent. She was symptomatically improved, but an attempt to test with the equilibration method was unsuccessful because she was made extremely nauseated and dizzy by the stimulation. In only this one case in the series was it possible to note the effect of the thyroid therapy, but the difference was sufficient to warrant the suggestion that, possibly, thyroid therapy would be beneficial in all of the cases.

In analyzing these cases it was found that the degree of disturbance in the basal metabolic rate in no way indicated the changes that were noted by the Bárány test. The changes are not constant, they are not localized to any one region, and are not of the

\* The author published an article on lowered bone conduction test in 1918.

same degree throughout. I believe that the tests demonstrate the fact that myxedema is a condition in which, besides the other changes, there are disturbances of response to stimuli in the eighth nerve tracts which coincide with response to stimuli in other nerve tracts. The exact nature of the pathologic condition causing this disturbance is a matter of conjecture. It may possibly be due to edema of the nerve, to the associated anemia, or it may be a combination of these associated with what may be called a psychical disturbance or high-grade weakness in the higher centers.

**Conclusions.** 1. In cases of myxedema there is a definite clinical vestibular picture which can be demonstrated by the equilibration tests and is in the nature of a delayed response to stimuli.

2. There is no relationship between the basal metabolic rate and the degree of this retardation.

3. The one case noted suggests the possibility that this clinical picture may be improved by thyroid therapy.

4. These cases are sufficiently interesting to warrant further investigation.

5. The foregoing data may be of very little value in itself, but add materially to the sum total of clinical information.

#### BIBLIOGRAPHY.

1. Boothby, W. M.: The basal metabolic rate in hyperthyroidism. *Jour. Am. Med. Assn.*, 1921, 67, 252-255.
2. Denker: Quoted by Lissner.
3. Hammerschlag: Quoted by Lissner.
4. Kendall, E. C.: Isolation of the iodine compound which occurs in the thyroid. *Jour. Biol. Chem.*, 1919, 39, 125-147.
5. Kendall, E. C. and Osterberg, A. E.: The clinical identification of thyroxin. *Jour. Biol. Chem.*, 1919, 40, 265-334.
6. Lissner, H.: The eye, ear, nose and throat in diseases of the thyroid and thymus. *Ophthal. Rec.*, 1916, 25, 433-440.
7. Plummer, H. S.: Interrelationship of function of the thyroid gland and its active agent, thyroxin, in the tissues of the body. *Jour. Am. Med. Assn.*, 1921, 77, 243-247.
8. St. Lager: Quoted by Lissner.
9. Sajous, C. E. de M.: *Internal secretions and principles of medicine*. 9 ed. Philadelphia, F. A. Davis Co., 1920, 1, 188.
10. Sajous, C. E. de M.: The endocrines in otology. *Laryngoscope*, 1921, 31, 659-672.
11. Sandiford, Irene: The basal metabolic rate in exophthalmic goiter (1917 cases) with a brief description of the technic used at the Mayo Clinic. *Endocrinology* 1920, 4, 71-87.
12. Scholz: Quoted by Lissner.
13. Wagner: Quoted by Lissner.

## THE TREATMENT OF THE SYPHILITIC LIVER AND HEART: A THERAPEUTIC PARADOX.

BY UDO J. WILE, M.D.,

UNIVERSITY HOSPITAL, ANN ARBOR, MICHIGAN.

THERE is no field of organic disease in which a prognosis under known given conditions is more difficult than in certain forms of visceral syphilis. While syphilitic infection, both acquired and hereditary, affects every viscus, there are two forms of visceral involvement which stand out, by reason of enormous relative frequency, to all others. These are the various forms of hepatic and cardiovascular syphilitic disease. Take away these two great incidents in the sequelæ of constitutional syphilis and the remaining clinical pictures of visceral luetic disease would play a relatively small part in clinical pathology and practice.

It is an accepted fact, and one which makes the whole problem of the diagnosis and treatment of visceral syphilis more difficult, that extensive disease may exist without any clinical manifestations. How common, indeed, is it to find at the post mortem in those dead from old age, accidents or from other causes, the evidence of syphilis in either liver or heart, or both, sufficient, apparently, to have caused marked clinical symptoms from their extensive pathology, unsuspected during life and revealed only at the necropsy. On the other hand how frequent is it to find serious disease with marked symptoms and relatively insignificant changes in the viscera at the post mortem. Prognosis, therefore, cannot be estimated except in a very general way by the apparent extent of damage which is manifest.

Viewing both the syphilitic liver and the syphilitic heart in their various phases as distinct entities, the therapeutic problem connected therewith is made increasingly difficult and more delicate, by the fact that under given like conditions no two cases can be accurately estimated with regard to prognosis.

The tremendous accession to our knowledge of the clinical pathology of syphilis during the last decade may be attributed to three distinct factors: The discovery of the parasite, the employment of the complement-fixation test to diagnosis and the introduction of arsenic compounds as specific therapeutic agents. An enormous awakening of interest in the whole problem of syphilis dates itself from the almost simultaneous appearance in medical practice of these important discoveries. The clinical pathology of syphilitic infection was broadened to include pictures which hitherto were accepted as either possibly being associated with syphilis or in some cases in no way connected with it. In no field of medicine have the boundaries of our knowledge been

extended further than in the newer conception of the syphilitic pathology of the heart and liver.

It is difficult to say that the clinical incidence of syphilitic hepatitis and cardiac disease is more frequent today than before, and their apparent greater occurrence, as well as the manifestations of neurosyphilis, is assuredly explainable upon the basis of more careful examination and the greater inclusion into syphilitic pathology of the various functional and organic diseases of these organs.

It may perhaps be recalled that with the introduction of the original salvarsan preparation, it was distinctly stated in the directions concerning its administration, that cardiac disease and other visceropathies constituted a contraindication to the administration of the drug. Striking results, however, in all forms of syphilis have led to the gradual abandonment of this early precaution, and today it may be stated that the vast majority of syphilitic patients, including those with diseased hearts and livers, at some time or other receive intravenous arsenic medication, in many cases even to the exclusion of other forms of treatment. The great danger, anticipated perhaps by few, of the employment of anything approaching a specific lay in the possibility of the development of a routine or of a "rule-by-thumb" method of treatment. For the most part it may, I believe, be stated that cases now regarded as those of syphilis are treated more or less routinely. Less regard is given the patient as an individual and smaller consideration given to that particular form of the disease which might be predominant in the clinical pathology. To a great extent the dispensary and the hospital, the need of treating a large number of patients in a given time, may be held accountable for the marked tendency to routine rather than individual treatment.

My own experience, I must confess, has not been entirely free from a tendency in this direction, and together with most others it has up to within a short time been my custom to employ, at least some time during the course of the syphilitic's life, one or more courses of intravenous arsenic medication.

It is particularly to the employment of this form of medication in connection with cardiovascular and hepatic syphilis that I would direct attention. I have been impressed, in discussing with older clinicians and in reviewing the literature of pre-salvarsan days, with the fact that either cardiovascular and hepatic syphilis have materially changed in their prognostic outlook, or else they were more intelligently and better treated in pre-salvarsan days than they are today.

The first premise, namely, that the picture has materially changed, is hardly tenable. We are therefore confronted with the second, and it would be well to inquire a little further into the factors and reasons for this. At a day when we know infinitely more concerning the pathology of cardiac syphilis and syphilis of the liver

in their various phases, at a time when we are possessed of improved methods of treatment, it at first may seem strange that our patients have not benefited accordingly.

In regard first to liver syphilis: The incidence of this may be said to be second only in frequency to that of syphilis of the heart. Considering its frequent accidental finding at the postmortem, it is evident that its incidence is far higher than might be deduced from clinical experience.

At the outset it might be stated that great confusion exists in the correlation between the pathologic and the clinical pictures of liver syphilis. The pathologic status of the condition, moreover, is a confused and debatable field among pathologists. It may be accepted that syphilitic hepatitis is due on the one hand to true involvement of the parenchyma, and on the other to primary involvement of the bloodvessels with secondary changes in the parenchyma. Undoubtedly most cases combine both features. In the strictly parenchymatous involvement we may now distinguish early and late forms. The early form is manifested by mild jaundice, transitory and significant only in its possible bearing upon later involvement. The severe form leads to acute yellow atrophy (*icterus gravis syphiliticus*). Various types of late hepatic syphilis are described as pathologic entities which do not in fact have their clinical analogues. To attempt to differentiate these as clinical pictures leads to inevitable confusion. In the gross and microscopic anatomy of hepatic syphilis certain facts stand out which if recognized and emphasized would lead to a more clear understanding of the clinical phases of the disease.

Late liver syphilis is either diffuse or circumscribed. The diffuse form, consisting of multitudinous infiltrates or miliary gummas, leads to an interstitial fibrosis. The more circumscribed form, consisting of isolated infiltrates and larger gummas, leads spontaneously or under treatment to localized fibrosis. The end-result in either case is identical, a more or less cirrhotic liver. The combination of these two forms is certainly more common than is either one alone.

Reconstructing the pictures clinically, therefore, one may have a small atrophic liver, with or without ascites, and resembling the Lacunne type, and a lobulated, either hypertrophic or atrophic liver, cirrhotic only in places, resulting from the circumscribed type. To this latter is given the name "*hepar lobatum*." The question of the size of the liver depends not so much upon the form of cirrhosis present as upon the time when the patient is seen. Hypertrophy may be seen early, to be followed later by atrophy, either spontaneous or under the influence of treatment. The clinical aspects in a given case depend upon the appearance in one case of tumor, and in the other of obstructive portal circulation leading to ascites, and the combination of these two pictures. There is no reason for a more



detailed description of the various symptoms which may or may not be present with syphilitic cirrhosis. These are familiar to all clinicians of experience.

There are certain mechanical factors present in these cases, however, which are of vital importance in the treatment and which affect the prognosis of a given case. The end-result of all syphilitic processes is a fibrosis. This fibrosis is materially hastened by energetic treatment. The process of repair in a parenchymatous organ in which fibrosis is going on depends upon its ability to recuperate by hypertrophy or by reproduction of its substance. The latter two functions are distinctly slow processes. Treatment, therefore, directed to a diseased organ in which the inevitable and ultimate result, both of the disease and of the treatment, is the production of a scar, should be of the type which leads to a slow rather than a rapid process of repair.

Brilliant results are occasionally achieved in one or the other type of syphilitic hepatitis by energetic and intensive treatment embodying the use of arsenic preparations. This cannot be denied. The consensus of opinion is that, compared with other forms of hepatic disease, syphilitic hepatitis has an admirable prognosis. I wish to concur in this view so far as it applies to the focal types, that is, gummosis hepatitis, *hepar lobatum* and to certain cases of the interstitial type. During the past ten years I have had a very unusual opportunity of studying many cases of hepatic syphilis in its various forms. Given equal conditions I have been struck with the great difference in the prognosis in the various cases of the same apparent type. From the standpoint of prognosis I find myself able to separate the cases broadly into three types: First, syphilitic cirrhosis in which gummosis tumors predominate. In a general way the prognosis of this condition stands out as the best of the three types. Second, combined gummosis involvement and extensive interstitial hepatitis. In this type as well as in the purely interstitial, non-gummosis type an apparent paradox in treatment occurs, particularly when such treatment is intensive. The patients improve with regard to their syphilis and get worse or die of their cirrhosis.

The apparent improvement which one may see in any case of visceral syphilis upon the institution of intensive treatment is not difficult to understand. The predominating clinical feature is but one phase of a widespread constitutional infection. A patient with hepatic syphilis, therefore, may feel decidedly better, his appetite returns, his vascular tone may be better, his color improve, and yet the predominating feature, the hepatic syphilis, may immediately become worse. I believe it may be stated that this is a general experience when the treatment is too intensive and when the process of repair is materially interfered with by the rapidity of connective-tissue replacement. It has been a

common occurrence in my experience for a patient with syphilitic hepatitis to develop his first ascites following the administration of salvarsan. Together with this there may be an intensification of the existing jaundice and a rapid disintegration of the liver, with increasing cachexia of the patient and early death by failure of metabolism. In the same type of case more conservative therapy in the form of mercury and iodide would have resulted in more gradual cicatrization, during which time compensatory hypertrophy might possibly have occurred in various unaffected portions of the organ. Portal obstruction might have been obviated and the patient's ultimate prognosis materially influenced for the better.

Another factor of extreme importance lies in the estimation of liver function. If it were possible by any accurate method to estimate the working capacity of this organ much might be learned with regard to what drug it could best tolerate. We must at this time be convinced of the fact that even to an apparently normal liver the administration of arsenic preparations is not without some danger. Indeed a particular type of jaundice, even in known non-syphilitic cases, can occasionally be produced, undoubtedly by the retention of arsenic in the liver, due possibly to preëxisting disease. With manifest lesions, therefore, in which one can with probability assume a marked degree of dysfunction, it becomes extremely hazardous to employ a substance which in itself may be said to be hepatotoxic, in attempting to alleviate the existing pathology. As an example of the effect of intensive régime embodying the use of arsenic preparations I beg to submit the brief histories of the following cases, which are typical of those of the class which I am describing and the study of which has led me to the above conclusions.

CASE I.—The patient, a man, aged thirty-three years, entered the hospital on June 13, 1919, complaining of swelling of the feet and legs and swelling of the abdomen. The syphilis was contracted fifteen years previously; treatment had been indifferent. One year previous to admission the onset of the disease appeared with a general anasarca. On examination he was found to be markedly emaciated and anemic, slightly jaundiced and to have an ascites and edema of the scrotum. The spleen and liver were both enormously enlarged, firm and hard, with no apparent indentations or nodes on the surface. There was no evidence of cardiac disease, but the lumbar puncture denoted associated cerebrospinal syphilis of the arterial type. In addition he had an old nasal perforation. This patient was given injections of salvarsan, six in number, with a most remarkable improvement in appetite and an improvement in his color and general well-being.

Notwithstanding the fact that he became a bed patient and had

proper diet and rest, his ascites became astonishingly increased. Immediately following his last treatment it became necessary to tap him almost every five or six days, and from June 22, 1919, to November 7 over 140,000 cc. of fluid were removed from this patient's abdomen in twenty-six paracenteses. A few weeks before the end of his stay in the hospital he was placed upon the cautious administration of mercury and iodide of potash, with most marked improvement in his ascites, and he was eventually discharged free of fluid in the abdomen. A recent report received from him indicates that he is now entirely well and has resumed his occupation.

His striking improvement in tone, appetite and general well-being can probably be ascribed to the effect of treatment on the syphilis existing outside of his liver. The more serious aspects of his hepatic disease were undoubtedly due to the mechanical causes resulting from a too rapid absorption of syphilitic tissue, its replacement by scar and the rapid shrinkage of the whole organ, associated with the possibility of a toxic effect of the arsenic on the remaining normal liver tissue. His ultimate recovery can without doubt be ascribed to the residual functioning portion of his liver, which fortunately escaped the ensnaring of the new-formed scar as well as the toxicity of the arsenic. I have in mind less fortunate cases, however, in which with far less clinical manifestations the increasing liver dysfunction, accompanied by ever-increasing ascites, led to a fatal issue.

Within the past month I have seen a case in an apparently healthy individual who, following two injections of neoarsphenamin, developed first the onset of apparent acute nephritis. Within two days after the onset coma developed, and this was succeeded by delirium and mania, cyanosis, slight jaundice and death after a stormy course in four days. The only clue to the hepatic pathology of this case lay in slight tenderness and rigidity over the liver region. At the autopsy the picture was that of interstitial hepatitis with beginning acute yellow atrophy and striking syphilitic changes of the heart and aorta.

As illustrative of the effect of salvarsan upon combined syphilitic cirrhosis and tuberculosis the following is cited:

CASE II.—The patient, a man, aged forty-two years, entered the hospital on April 11, 1919, complaining of jaundice and loss of weight and weakness. His syphilis dated twenty years previously, at which time he had had indifferent treatment. Two years previous to admission he became slightly jaundiced and began to lose greatly in weight and strength. On examination he was found to have an extremely large liver, very hard and irregular, giving one the impression of linear scarring on its surface. The

spleen was markedly enlarged. The heart was negative to physical examination, but there was an extensive pulmonary tuberculosis demonstrated by physical signs and by frequent sputum examinations. Following very cautious administration of neoarsphenamin, the largest dose being but 3 gm., the patient's abdomen began to fill. Paracentesis yielded about 1000 cc of fluid and was followed by rapid refilling of the abdominal cavity. Following this the patient rapidly deteriorated, became more markedly jaundiced, extremely weakened with rapid loss of weight, and exitus occurred five or six weeks later in stupor, with extreme emaciation and ever increasing anemia. At the postmortem chronic pulmonary tuberculosis, intestinal, mesenteric and peritoneal tuberculosis and miliary tuberculosis in the liver, spleen and pancreas were found. In addition to this he had a typical *hepar lobatum*, extensive syphilitic cirrhosis and syphilitic myocarditis and aortitis, the latter two not suspected during life. With the combined picture of extensive tuberculosis it is perhaps difficult to say in this case that the outcome would have been different had the treatment been more conservative. I am impressed, however, from a rather large experience with cases in which tuberculosis and syphilis are combined, that neither is markedly benefited by an energetic treatment employing the use of the salvarsan derivatives.

In the absence of laboratory data giving us a clue as to the functional capacity of the normal and diseased liver it seems injudicious to employ in the treatment of any form of syphilitic disease any form of therapy in which the ultimate process of the disease is anticipated, so to speak, by the effect of the treatment. A gradual resorption seems to result in a better functioning organ than follows a rapid absorption and disintegration of the diseased processes. Treatment, therefore, leading to the former would seem to be more desirable and a more rational course to pursue. I believe that salvarsan has no place in the treatment of liver disease. That it can, in certain cases, produce brilliant results, and this must be admitted, is due not to the treatment but rather in spite of it and speaks for the functional reserve of the diseased organ in the particular case. Unfortunately, however, this reserve cannot be estimated. The dictum "Treat intensively and intelligently" in syphilitic disease requires, I believe, modification when the disease presents itself with predominant findings in the liver. The intelligent handling of such a case consists not in the intensive form of treatment but in a more conservative plan, remembering the mechanical processes which might prevent a happy result and with due regard to as yet immeasurable physiologic functioning.

Syphilis, as it affects the heart, has fully as diversified a group

of pathologic pictures as occurs in the liver. As in the latter organ, however, the pictures represent different phases of the same rather than different conditions. Syphilitic myocarditis, for example, viewed pathologically, may be the result of diffuse interstitial infiltration, the disintegration and absorption of multiple minute gummas, degenerative changes near the terminals of the coronary arterioles, and muscle degeneration and replacement following obstruction or obliteration of the minute coronary vessels (myelomalacia).

Clinically, however, these varied pathologic processes present themselves as more or less severe grades of myocardial disease. Quite apart from these are the various pathologic findings in and about the base of the aorta and the aortic ring as well as those on the aortic flaps, giving the clinical picture of varying degrees of aortitis and aortic regurgitation. Coronary involvement, a still third pathologic and clinical picture, is probably so universally associated with myocardial disease that its clinical syndrome may be regarded in the symptom-complex of myocarditis. Endocardial changes involving the other valve cusps have been described, but are of such rare occurrence that, viewed from the standpoint of frequency, they may be disregarded here. As Harlow Brooks has properly pointed out, the regular, almost universal association of myocardial disease with aortic aneurysm in any form, and aortitis, brings these two conditions into a prominent place in the consideration of cardiac syphilis. Broadly speaking, therefore, clinical syphilis of the heart resolves itself into a consideration of the symptoms dependent upon myocarditis, aortic regurgitation, aortic aneurysm, syphilitic aortitis and coronary disease. It is highly probably that none of these conditions exists alone. Disease of the heart muscle may be said to be almost concomitant sooner or later with all of the aforementioned. As Brooks and others have properly brought out, the treatment, of the syphilitic heart resolves itself into two distinct factors; the syphilitic infection on the one hand and the cardiac defect on the other. These two completely distinct problems suggest at once that the proper management of such cases necessitates a knowledge on the one hand of the physiologic pathology of the heart and its treatment and on the other hand a broad comprehensive knowledge of the systemic disease. Herein, I believe, lies the explanation of the fact that today medical men are not as well equipped for, nor are giving as intelligent treatment to such cases as were their predecessors of two or three decades ago. Today not only has the periphery of our knowledge concerning syphilis been tremendously extended, necessitating the development of specially trained men in this disease, but the field of internal medicine has reached far into the realm of biochemistry and physiologic pathology. The inevitable result has been that the syphilologist, highly specialized but

lacking modern diagnostic methods of cardiac disease, treats the cases from the standpoint of the general infection, and too little attention is paid to the predominating dysfunction, namely, the diseased heart. Viewed from the other side, the internist, fully equipped with modern methods of cardiac investigation, naturally finds his chief interest in the predominating feature, namely, the diseased heart, and the extensive associated constitutional features of the case are oftentimes slighted in its treatment.

Surely a happy medium suggests itself for the correction of this natural tendency to error. The cases should be studied and treated from the standpoint, first, of the disease, and secondly, from the cardiac defect. In hospitals the ideal can be achieved when the case can have the benefit of the combined efforts of those properly equipped.

It is entirely apart from my purpose, and I am unequipped by training, to discuss the treatment of the cardiac defect in a given case.

From a rather extensive experience, however, in the management of such cases as have been described above, in collaboration with those admirably equipped to treat the cardiac defect, I have reached some very definite conclusions as to what constitutes the intelligent treatment of cases of cardiac syphilis.

My experience with salvarsan in these cases dates almost from the time of the introduction of the drug, notwithstanding the instructions which were sent out with the early packages, that cardiac disease constituted a contraindication. As I stated before I believe this fundamental error is largely practised, and few cases of syphilis are, indeed, denied at some time during their course the benefits which might be derived from the intravenous administration of salvarsan. Indeed so universal has this become that patients actually demand that form of treatment and view with suspicion any tendency to withhold it from them.

Even with due regard to the warnings concerning the contraindication of the drug, many cases of unsuspected non-symptomatic cardiac syphilis receive salvarsan; notably as is true of the very early cases of myocarditis in which the symptoms only become manifest after the treatment. It must be recalled at this point that actual cardiac syphilis in the very early months of the infection, coincident, indeed, with the exanthem, may be present either without any symptoms or with such slight clinical findings as arrhythmia and tachycardia. This last group of cases, however, probably does not present the serious problem that the later ones, in which the cardiac defect is the predominating feature of the case do, and brilliant results perhaps may be achieved in these cases with the intensive form of treatment. I have in mind, however, one case in which such treatment resulted in heart-block and in a marked accentuation of early suggestive features, so that

well-developed myocardial disease resulted in the first year of the infection.

In the early forms of myocardial disease also, and in many cases of aortic regurgitation, both compensated and decompensated, I have seen extraordinarily happy results from the use of the intensive administration of intravenous arsenic medication. As in syphilis of the liver, however, it is impossible to say in a given group of cases just exactly how an individual may react. Thus it has been my unfortunate but instructive experience to note in cases in which a happy result might be expected, intravenous medication has resulted in decompensation or acute dilatation and failure in the myocardial and aortic groups. Two cases of aneurysm in my experience have ruptured, and numerous cases of aortitis and of coronary disease have become unfortunately worse in regard to the cardiac aspect of their condition.

It is not difficult, I think, to find the source of the explanation for these unfortunate accidents. Taking the group of myocardial cases and discussing them now solely from the standpoint of syphilis, I have been impressed with the fact that these hearts untreated are frequently better functioning organs than when subjected to violent intensive therapy. There is at least some reason for believing that mechanical causes may explain this. The syphilitic infiltrates, particularly in the more diffuse form, while they unquestionably materially weaken muscle tone and function, have, as is well known, a certain degree of elasticity. Their rapid replacement or disintegration may lead to actual gaps and to such a rapid fibrosis that many otherwise normal heart-muscle cells disintegrate or are snared off in the cicatrizing process, and the result is further embarrassment, most often manifested by acute dilatation. Compensatory hypertrophy is, perhaps, nowhere seen so admirably as in the heart muscle. A compensatory hypertrophy, however, requires time, and means the slow absorption of diseased process and the slow recuperation of non-diseased muscle fibers. This, I believe, can be achieved, and is when the syphilitic heart is treated from the standpoint of its syphilis, at least slowly, and due attention is paid to it from the side of the defect. Not only may it be stated that the intensive treatment of the syphilitic heart is injudicious because of mechanical reasons, but such treatment is, indeed, at entire variance with what might properly be regarded as the effort to keep and enhance a cardiac reserve, which is the aim of the treatment directed to the defect alone. Another factor, at least of some possible bearing in producing acute failure, is the introduction into the blood stream of a not inconsiderable amount of fluid. This applies, of course, to preparations of the so-called "old salvarsan" derivatives, which necessitate the introduction of 100 cc or more of fluid.

It has been possible for me, in individual cases in which for

other reasons I have withheld salvarsan and its derivatives and employed more conservative forms of treatment, as well as in groups of cases in which I intentionally withheld the drug, to compare such groups with those treated more intensively. In both types of cases I have had the benefit of expert advice on the part of my associates in internal medicine who have treated the cases with me from the standpoint of the cardiac defect. In not a single case that I can recall of either aortitis, myocarditis or aneurysmal disease can it be stated that any untoward accident happened immediately following the institution of the treatment. In fact the reverse may be said to have been the general rule. Improvement, slow to be sure, almost invariably took place. On the other hand it must be stated that the improvement in the patient's general condition was not so striking in cases treated more conservatively, for example, with mercury and iodide. It has been a not infrequent occurrence for patients treated intensively to have an immediate betterment of their general condition, a better color and a feeling of general well-being. This, in every case, I believe, is due to the effect of the treatment upon foci elsewhere, which have been dispersed, and to a general effect upon the circulation. Such a change is not so apt to occur when iodide and mercury are given—at least the change, if it does occur, is usually later, and particularly after the drugs have been withdrawn.

The remarkable improvement in general following the arsenic treatment has often been followed in some cases by a most rapid deterioration, with evidences of accentuation of the original cardiac defect. Here one can only surmise at two possible explanations, both of which are probably factors: First, that the syphilitic products have been too rapidly replaced by scar tissue, or, second, that their rapid disintegration has produced a chemical change deleterious in its effect on the local lesion.

Here, therefore, as in liver syphilis, we are confronted with the remarkable paradox that the patient gets well or better of his syphilis, and may die as the result of the dispersion of his syphilitic cardiac lesion.

I should like briefly to summarize a few cases illustrative of the above conditions:

CASE I.—*Syphilitic Aortitis*. The patient, a man, aged forty-four years, entered the hospital on March 23, 1920, having been transferred from the department of medicine with a diagnosis of syphilitic aortitis. He denied knowledge of syphilis. His present trouble manifested itself as shortness of breath two years previous to admission. This became more marked until, on admission, he could not lie down for more than an hour at a time, nor could he give himself the slightest exertion without developing a marked



dyspnea. In addition he had considerable palpitation and some precordial pain. The clinical findings were those of aortitis and typical regurgitation. The patient received two injections of small doses of neoarsphenamin, only 2 gm. to which he immediately reacted with marked improvement. His symptoms and pains disappeared, his dyspnea, while present, was markedly less, and in a short time he was dismissed from the hospital for observation. Within a very brief time the patient returned completely decompensated, and it was only with the greatest difficulty that his reserve was brought up to such a point that he could again leave the hospital. His second respite was even shorter, and he has returned twice since, both of which times he was in so desperate a condition that it was believed he could not recover. At the present writing he is still living but without any reserve, and practically bedfast.

CASE II.—*Tabes Dorsalis, Aortitis, Aneurysm of the Arch, Both Unsuspected.* The patient, aged forty-six years, entered the hospital for treatment for syphilis. His infection dated back some twenty-four years, at which time he had had indifferent treatment. His present trouble began four years ago with failure of eyesight and pains. On examination he was found to have a typical tabes dorsalis, with all the classical findings. This patient received but two injections of arsphenamin, 3 gm. and four and five-tenths respectively. The second injection was followed by severe headache and attacks of dizziness as well as numbness and cold sweat. He became very cyanotic and within a few days was bedfast. At this time the first suggestion of a cardiac defect manifested itself in marked arrhythmia, weakness of the pulse, general asthenia and cyanosis and signs of cardiac dilatation. He continued in this condition for about three weeks and died suddenly in bed during the night. At the post mortem he was found to have aortitis, aneurysm, myocarditis and syphilis of the cord and brain.

This case I believe to be extremely interesting and valuable, as showing the regular association of cardiovascular and other forms of visceral syphilis, with the predominant findings those referring to the nervous system. I have seen frequent examples of this, and their occasional occurrence has made me more cautious in the use of intensive intravenous medication in cases of neurosyphilis until I have been completely satisfied and have been assured by my internist colleagues that such patients are free, or apparently so, from evident cardiovascular disease.

CASE III.—*Syphilitic Aortitis and Myocarditis.* The patient, aged forty-four years, entered the hospital, having been referred by the department of internal medicine with a diagnosis of old syphilis and aortitis. His infection dated twelve years previous

to his admission, and treatment had at that time been indifferent. Two years previous to admission he noticed shortness of breath, weakness, dizziness and difficulty in walking. These symptoms were accompanied by sharp pains in the right side of his chest. The clinical findings were those of aortitis and regurgitation, well compensated, otherwise negative. This patient received seven injections of neoarsphenamin, the largest being only 3 gm. and the smallest. 1+. These injections were decidedly small, as I had begun to feel when he was treated that maximum dosage must be avoided in these cases. Following his injections the patient developed typical attacks of angina pectoris, these occurring very frequently. They were associated with cyanosis, collapse and syncope, so that it was feared that he might die any time during the attack. During the patient's stay in the hospital, some eight weeks, he was completely bedfast. Only after all medication had ceased and the strictest attention was paid to the cardiac defect as such did he show any sign of improvement. Under iodine and mercury, which were administered during the latter part of his stay, he gradually improved, so that the attacks finally completely ceased, his dyspnea disappeared and he was able to be discharged from the hospital.

These cases are but a few of many which I have seen, both in the hospital and private practice, in which the result, frequently fatal, more often deleterious, could justifiably, I think, be ascribed to the type of the treatment employed.

I am a most ardent advocate of the use of arsphenamin in the treatment of syphilis. However, notwithstanding the fact that brilliant results may sometimes be achieved in cases of severe visceral disease, I am of the opinion that it should not be used as a routine measure in the treatment of cardiac and hepatic syphilis. When indicated in these two conditions it may be used with reasonable safety in those cases which have responded to a previous administration of mercury and iodide. The great difficulty and the necessity for taking a positive stand lies, I believe, in our inability to properly estimate the new case from the standpoint of prognosis when it is first seen. With everything in its favor apparently, from the extent of the lesion, the shortness of its duration and the general well-being of the patient, a case of cardiovascular or hepatic syphilis may well turn out to be one with serious or even fatal sequelæ. The converse, of course, must be admitted, that cases with the most serious aspects from the standpoint of the extent of lesions and general condition of the patient may react favorably to intensive treatment.

In mercury and iodide we have two drugs admirably suited for the treatment of cardiovascular and hepatic as well as other forms of visceral syphilis. Their action is slow, and this, I believe,

is desirable. In all cases their use should be combined with the intelligent treatment of the diseased heart, and this can only be done in collaboration with the internist. On his part the internist may find useful in the management of such cases the very special knowledge which the syphilologist has of the various salts of mercury, their different uses in different types of individuals, the advantage of frequent change and more particularly the management of the constitutional side of the infection.

In the employment of newer and more potent arsenic preparations, which are constantly being introduced, I believe it is safe to predict that even greater disaster and more frequent fatality may occur when these drugs are used in the treatment of the visceral forms of the disease. The syphilized liver and heart, in whatever stage of the disease, from clinical experience at least, seem to do better when the process of repair is slow and when no great strain is placed upon their normal functioning activities.

---

### ACUTE LUNG ABSCESS TREATED BY THERAPEUTIC PNEUMOTHORAX.

BY HERBERT M. RICH, M.D.,

DETROIT.

THE danger and the high mortality of surgical drainage of pulmonary abscess lend importance to the discussion of any method which will improve our results in these cases. It has seemed worth while, therefore, to report the following experiences with the hope that as case-records accumulate we shall be able to steer a safe course in the treatment of acute pulmonary abscess. The cases here reported are all non-tuberculous.

**Nomenclature.** The term lung abscess is a somewhat ill-defined expression for intrapulmonary pus. It may be diffuse or circumscribed, acute or chronic, gangrenous or not. It is frequently an extension from a purulent process in the neighboring tissues, as empyema, lateral or interlobar. Its etiology has many items. For the purpose of this paper, pus in the lung, the result of burrowing from an interlobar empyema, ultimately reaching a bronchus, is called a lung abscess. There seems to be no single pathologic term in English which will describe this condition. Other processes producing free pus in the lung are included under this term, the etiologic items being mentioned in the separate case reports. This explanatory paragraph is inserted because of the lack of satisfactory nomenclature for these conditions, causing confusion in the mind of the reader.

CASE REPORTS. CASE I.—Miss B., stenographer, aged twenty-one years. Bronchopneumonia. Lung abscess. Pneumothorax successful. Recovery.

First seen October 16, 1919. Had been ill with bronchopneumonia six weeks; fever, chills, pain in right chest until it "broke." For one week there had been daily evacuation up to one pint of pus, extremely foul smelling. Temperature, range  $101^{\circ}$  to  $104^{\circ}$  F. Great prostration and weakness. Physical findings showed impaired resonance over the lower lobe right lung, surrounded by zone of moist rales of great variety. No signs of fluid or tuberculosis. Diagnosis of lung abscess or interlobar empyema was made and compression of the lung by means of therapeutic pneumothorax advised.

Entered Harper Hospital, Detroit, October 21. Temperature,  $102^{\circ}$  to  $104^{\circ}$  F. Weight, 84 pounds (usual weight, 96 pounds).

October 24. Pneumothorax attempted in fifth interspace of the right axilla. Pleura very thick; strong pleural reflex with severe pain; 50 cc sterile air injected, but was obliged to discontinue because of spasm of diaphragm due to pleural reflex.

October 25. Pneumothorax in third interspace; 300 cc air introduced. Followed by only slight pain, but in a few hours by greatly increased cough and expectoration. Seemed much better two days later, but foul sputum continued in small quantity.

October 30. 250 cc of sterile air.

November 6. 300 cc of sterile air followed by some pain at the base of the right lung. Cough and expectoration disappeared.

November 9. Patient left hospital apparently well. Weight, 90 pounds. Sputum repeatedly negative for tubercle bacilli. Frequent reports from the patient since up to June, 1921: Has remained in good health and without cough or expectoration.

CASE II.—A. S., lawyer, aged forty-eight years. Simple cold followed by lung abscess. Successful pneumothorax. Recovery.

Never ill in bed since infancy.

October 23. Had cold. October 25. Went to Oklahoma. Had fever, chills, bad cough, sputum became purulent about November 2. First seen November 6. Temperature,  $100.8^{\circ}$  F. Paroxysmal cough, odor of sputum extremely foul. Physical examination showed an impaired resonance and bronchial breathing in the right axilla, at 4th and 5th ribs, surrounded by a zone of coarse and fine moist rales. Sputum negative for tubercle bacilli.

Entered Harper Hospital November 12. Temperature,  $101^{\circ}$  F. Roentgen ray. "Fluoroscopic examination: Chest in erect position shows abscess described previously in the right upper lobe. There is definite evidence of cavity formation. The right upper lobe is apparently immobile. Free excursion of diaphragm on both sides." (Allison)

Pneumothorax, anterior axillary line, in 4th interspace; 275 cc of sterile air introduced.

About twenty-four hours later the patient had a severe paroxysm of coughing, with evacuation of a large quantity of sputum and alarming exhaustion. This was the last of the severe paroxysms of cough.

November 14. Pneumothorax attempted. Slight pleural shock from the needle used in giving local anesthetic. No gas given.

Patient continues to improve. Temperature not above normal after November 19. Left hospital November 28. Entirely free from symptoms; last seen June, 1921.

This was a case of interlobar empyema, opening into a bronchus, following a simple cold. Nothing else so far as I know can answer the roentgen-ray description of a cavity partly filled with fluid, later disappearing entirely. Evacuation was induced by very slight compression and recovery was prompt and satisfactory.

CASE III.—Miss K., aged nineteen years. Appendectomy with drainage. Influenza. Bilateral bronchopneumonia. Lung abscess. Pneumothorax successful. Death.

Never ill in bed until January 10, 1920. Acute suppurative appendicitis; operated in local hospital; drainage established.

January 25. Said to have had influenza followed by double bronchopneumonia. Temperature normal in ten days, then chill, fever, pain in region at base of right lung. First seen February 22. Temperature, 104° F. Patient emaciated, pale, panting, anxious, very weak, pulse 140. Open wound in abdomen with foul discharge. Exhausting paroxysmal cough, raising at intervals 4 to 6 ounces of sputum, extremely foul odor. Examination of chest: Relative dulness in irregular area of lower right lung. Many coarse, moist, bubbling rales. No evidence of fluid.

Entered Harper Hospital, February 24. Temperature, 101.4° F. Pulse, 132. Symptoms and signs unchanged. Sputum, negative for tubercle bacilli; pneumococcus, Type IV.

March 1. Symptoms continued without improvement, so compression was undertaken as a last resort. Pneumothorax needle introduced in 4th intercostal space of right anterior axillary line. Pleura thickened; no oscillation; in third intercostal space, good oscillation and 350 cc of sterile air introduced. Later, coughed up several ounces of foul sputum. Felt relieved and coughed much less until death the following day from asthenia. No autopsy permitted.

It is obvious that the fatality in this case was not due entirely to the lung abscess nor to the pneumothorax.

CASE IV.—Mrs. T., aged thirty-one years; pregnant five months; influenza. Interlobar empyema; evacuation into bronchus; successful pneumothorax; recovery.

Seen February 16, with recurrent paroxysmal cough and great expectoration of five weeks' duration following influenza; pregnant five months; paroxysm very severe, leaving patient exhausted, limp and expecting to die. Previous history unimportant. Signs of abscess in lower lobe right lung.

Entered Harper Hospital February 16. Temperature,  $103^{\circ}$  F. Pulse, 120. Urine negative. Sputum negative for tubercle bacilli. Pneumococcus, Type IV. Blood: 16,000 white cells, polynuclears, 52 per cent. Patient did not improve.

February 18. Pneumothorax needle inserted in midaxillary line, 4th intercostal space. Gave 550 cc of sterile air. Very severe paroxysm of coughing about six hours after first injection of air. Emptied out a pint of purulent fluid. Much relieved. Temperature reached normal four days later. Never had severe cough after that day. Second injection in seven days, February 25. Left hospital March 3, free from symptoms.

June, 1921, reported quite well by family physician, never having had any return of symptoms.

In this case the pathology was probably an interlobar empyema burrowing into the lung.

CASE V.—Mrs. P., aged thirty-one years. Influenza; pneumonia; lung abscess in upper lobe. Spontaneous recovery.

Two children. Never ill since childhood until influenza in January, 1920. Pneumonia followed. First seen three weeks later, February 10. Terrific paroxysms of coughing with large quantities of fluid, offensive pus. Signs of interlobar empyema, probably between upper and middle lobes on right.

No roentgen-ray taken then. Patient reluctant to go to hospital and a few days later began to improve and ultimately recovered. Roentgen-ray six weeks later showed most of lung clear, the only signs of the recent trouble being increased linear markings in the right lung.

June, 1920. In good health.

This was an instance of so-called spontaneous recovery.

CASE VI.—Miss D., aged twenty-nine years. Similar to Case V. Social worker, never ill before. Seen February 15, 1920. Paroxysmal cough, bringing up at times more than a teacupful of purulent sputum. Sputum had pinkish tint. Temperature,  $102.8^{\circ}$  F. Profuse sweats. Profound exhaustion. Refused hospital. Gradual improvement. Left city several weeks later, in good condition.

Another spontaneous recovery.

CASE VII.—A. F. aged forty-two years. Meehanie. Bronchopneumonia followed by lung abscess. Successful pneumothorax. Recovery.

Entered Harper Hospital, service of Dr. Freund, April 4, 1920. Complaint—fever, cough with blood-tinged sputum, dyspnea, weakness. Previous history negative. His symptoms have been gradually developing for ten days. Physical examination showed extensive pyorrhea and many crowned teeth which later proved to cover five dental abscesses, one very large. There was dullness over the upper half of the right chest and in the upper axilla. Whispered voice increased over a part of this area. Breath sounds were variable, distant in some areas with bronchovesicular predominant. Fine and coarse rales. Temperature range, 101° to 103° F. Wassermann negative. Temperature down to normal on sixth day with 101° F. in evening. Continued to have 99° to 103° F. daily. Sputum negative for tubercle bacilli; pneumococcus, Type IV. Symptoms continuing and patient becoming weaker. On May 20, therapeutic pneumothorax was induced. Puncture in 8th intercostal space below point of scapula. 550 cc of sterile air given.

May 23, 200 cc of sterile air were given. Patient improved promptly. Temperature approached normal; cough and expectoration less; appetite and strength improved.

May 29. Roentgen ray report: "Outer fourth of upper right lung filled with an area of density, extending toward the midlung field opposite to the third interspace. There is evidence of a partial collapse of the lung, the extra density is probably due to thickening of the pleura." W. A. Evans.

June 3. 200 cc of sterile air injected.

June 12. Patient discharged from hospital, apparently well. Seen on August 1 and had continued to that time without symptoms. Had gained 42 pounds.

The sequence in this case was undoubtedly first multiple dental abscesses; second, lobar pneumonia; third, lung abscess.

CASE VIII.—Mrs. C., aged twenty-eight years; pregnant seven months. Influenza. Lung abscess. Compression successful. Recovery.

February, 1920. Influenza, followed by lung abscess in left lower back. First seen March 12. Had been ill six weeks. Daily evacuation of twelve to fifteen ounces of foul pus; very weak; no fever. Also pregnant and fearing miscarriage from cough. Usual signs of abscess. Had had three "dry" punctures. Pneumothorax with 500 cc of air injected on March 13. By March 17 the twenty-four hour amount of sputum was reduced to five ounces. On March 18 there was none. Practically no cough after this. Patient left hospital on March 21, and resumed household duties.

March 30, 500 cc of air given. Has remained well since and been successfully confined.

CASE IX.—Mrs. P., aged thirty years; operation on cervix; lung abscess; unsuccessful attempt at pneumothorax; surgical drainage; death.

Had two children. Never ill. Was operated for laceration of cervix, leaving hospital July 24, 1920, convalescent. One week later pain in lower right chest; sudden onset. Respiration painful. Temperature, 103°F. Marked dyspnea. After continued fever for six days the temperature dropped and a pint of blood-stained, foul-smelling purulent sputum was expectorated. Two days later fever again appeared and septic temperature continued until first seen with Dr. George E. McKean, August 26. At this time she had physical signs of an abscess of lung under right breast. Roentgen-ray showed a fluid level, the lateral oblique plate showing that the abscess anteriorly was very near the external pleura.

August 28. Therapeutic pneumothorax in the fourth intercostal space, midaxillary line, 500 cc of sterile air injected. Pleura distinctly thickened. Violent coughing following with considerable subcutaneous emphysema. During the following twenty-four hours the abscess perforated into the pleural cavity under the right breast. The condition was then complicated by this pyopneumothorax, which was operated under local anesthesia by Dr. Max Ballin, August 29. Ample drainage was established, but the patient did not rally and died August 31 from pulmonary edema.

In this case there was a septic embolus from the cervix. The abscess was near the periphery of the lung. To attempt pneumothorax in such a case is undoubtedly a mistake.

CASE X.—Mrs. B., aged twenty-five years. Tonsillectomy; lung abscess for five months. Pneumothorax successful. Recovery.

Tonsillectomy in December, 1916. Four days later had pneumonia, lasting two weeks. Shortly after began expectoration of foul-smelling, purulent sputum. Had cough, pain, sputum, occasionally bloodstreaked. Coughed more on first rising in morning; also when lying on right side. This continued all winter. Was slightly better in summer, but symptoms reappeared in the fall, 1917. Went to California, January to March, 1918. Seen first after return. Temperature, 100.6°; pulse 120, sitting; weight, 203 pounds. Complaint, pain in right upper thorax; night-sweats, cough and foul sputum continue.

May 27, 1918, therapeutic pneumothorax induced by 300 cc of nitrogen in the right pleural cavity. Was followed by severe pain for one day. No increase in amount of sputum.

June 4. 550 cc of sterile air. Had considerable pain and some subcutaneous emphysema.

June 20. No fever, cough or foul sputum since last injection.



Gave 400 cc of sterile air. Had pain in back and neck for one day. No more night-sweats. This was the last treatment. Symptoms disappeared and there has been no reappearance up to December, 1920.

This abscess could hardly be called acute, and compression was obviously imperfect, owing to adhesions. It shows that the pneumothorax method may be useful even in the presence of adhesions, and that complete collapse of the lung is not necessary in every case.

**Spontaneous Cure.** It should be pointed out that a certain number of cases of pulmonary abscess empty out through a bronchus and recover perfectly. I have seen 3 such cases, and the medical profession of nearly every community has traditions of such happy cures. In 1 case, which I studied three years after such spontaneous evacuation, neither physical examination nor roentgen ray revealed any evidence of permanent change in the lung. This abscess followed a tonsillectomy and had been active four weeks. The spontaneous evacuation occurred one hour before the operation for surgical drainage was to be done.

In the 3 cases of spontaneous cure here noted the abscess in each case was in an upper lobe. It seems certain that spontaneous cure is much less likely to occur when the lesion is in a lower lobe. While these do often discharge into a bronchus, their evacuation is usually only partial and the coughing necessary is so severe and exhausting as to be highly alarming. The inverted posture assists the cough in emptying the contents of the abscess, but in the event of a tortuous fistulous track does not help greatly. In the present series of cases inversion of the person was only occasionally useful.

It would seem then that while upper lobe abscesses may be spontaneously cured it is highly improbable that those in the lower lobe will. It is extremely important that one should not be misled in prognosis by the fact that a lower lobe abscess is discharging pus through a bronchus. This does not mean that efficient drainage is established, and while waiting for spontaneous cure one may allow the time to pass in which the lung could be successfully compressed and a perfect cure effected.

**Time for Operation.** In this series the oldest abscess successfully treated was of eight weeks' standing with the exception of Case X.

In Tewksbury's series of 10 acute cases the latest successful one was of six weeks duration. The most advantageous time would seem to be between the second and fourth weeks. The development of adhesions to the outer chest wall will depend largely on the position of the abscess. When near the periphery, adhesions will quickly form and perforation into the external pleural cavity is the event to be expected. It is doubtful if compression should

be undertaken in these cases. On the other hand abscesses near the hilus, where most difficult to reach for surgical drainage and where bronchial fistulæ are most likely to persist, are easily and promptly cured by a mild compression. Since the therapeutic pneumothorax is painless and harmless the question arises whether one is ever justified in carrying expectant treatment more than two weeks.

One factor which must be insisted upon is the continuance of the treatment until the lesion has had time to heal. While a short compression may be followed by the most happy results, one should maintain the compression for four weeks in acute cases and much longer in chronic cases. Such chronic cases, however, may safely leave the hospital in a few days, doing light work and merely returning at regular intervals for refills.

**Etiology.** Of the 10 cases here cited:

One followed a pelvic operation, the colon bacillus predominating in the lung abscess, undoubtedly a septic infarct.

One followed a simple cold.

One followed tonsillectomy under ether anesthesia.

Two followed bronchopneumonia.

Four followed the influenza-bronchopneumonia syndrome. In several of these cases the roentgen-ray findings made it certain that interlobar empyema preceded the abscess formation.

Eight of the 10 cases were women; 2 men. All were adults twenty-one to forty-eight years. None of these gave a history of previous lung disease. In fact, in none of these patients was there any history of previous severe illness of any character. Repeated examinations for tubercle bacilli were made in every case, and all were negative.

The time of development varied greatly. In Case II, a simple cold developed fetid sputum in five days. Two cases of bronchopneumonia "broke" in about six weeks. The lung infarct following operation on the cervix, developed two weeks after operation (Case IX). In none of the influenza cases could the time be accurately fixed. In each of these symptoms ultimately showing abscess developed about three weeks after the onset of the pneumonia.

**Prognosis.** Under the older methods of treatment the outlook for a case of pulmonary abscess is indeed discouraging. Spontaneous recovery is very uncertain and is not due to any treatment. Foreheimer quotes the figures on 133 cases with less than 10 per cent recovery and death in 64 per cent. Other figures are more favorable for small numbers of cases. However, the surgical treatment involves a highly difficult and dangerous operation, and Lord makes the statement that "incomplete cure is the rule." Combining the cases reported by Tewksbury with those here detailed, there are 20 cases of acute abscess with 16 instances of prompt and complete recovery, or 80 per cent.

**Comment.** The literature on this form of treatment in abscess is limited. The procedure was first proposed by Forlanini, and later, 1910, he reported a case of chronic lung abscess of six years' duration following croupous pneumonia. Treatment was continued twenty-five months with great amelioration of symptoms. He does not record the treatment of any cases of acute abscess, but Schmidt, in 1908, in reporting experience with pneumothorax in a variety of conditions, mentions its use in three cases as follows:

1. "Aspiration-pneumonia," six months' duration. One injection of 1000 cc of sterile air. Much better in two weeks; discharged from hospital cured in four weeks.

2. "Fetid bronchitis," several years' standing, worse last few weeks. No response to previous treatment. Tubercle bacilli present in sputum. Prompt improvement under treatment, which consisted of one injection of 300 cc of sterile salt solution. Patient gained eighteen pounds in five weeks. Discharged cured. Seen two years later with no return of symptoms.

3. "Fetid bronchitis," with induration in right lower lobe. Had been ill without improvement from September to February (five months). One injection of 1200 cc of sterile air. Patient left hospital in one month, apparently well, seen thirteen months later, no recurrence.

Whether these cases should be classed as bronchiectasis or lung abscess is difficult to say. The report of cure by a single injection, one by the use of salt solution, is at least interesting and stimulating.

Tewksbury in two papers reports in all 10 acute cases with 8 recoveries and 2 deaths. In the fatal cases the compression was not directly connected with the cause of death, as both cases had serious disease aside from the lung abscess.

**Summary.**—Ten cases of pulmonary abscess are reported. Eight were treated with therapeutic pneumothorax. There were 8 complete recoveries and two deaths—two spontaneous recoveries.

The experiences here related corroborate those of Tewksbury in every particular. Acute pulmonary abscess may be promptly and completely cured by therapeutic pneumothorax. A possible exception should be made in those cases where the abscess is located near the periphery of the lung.

#### REFERENCES.

1. Tewksbury, W. D.: Jour. Am. Med. Assn., March 10, 1917.
2. Tewksbury, W. D.: Jour. Am. Med. Assn., February 2, 1918.
3. Simon and Swezey: Am. Rev. Tuberc., 1918.
4. Schmidt, A.: Beit. zur. Klinik der Tub., 1908, Bd. 9.
5. Forlanini: München. med. Wchnschr., January 18, 1910.

## REVIEWS.

---

ORAL ROENTGENOLOGY. By KURT H. THOMA, D.M.D., Assistant Professor of Oral Histology and Pathology, and Member of the Research Committee, Harvard University Dental School; Oral Surgeon, Robert Breck Brigham Hospital, etc. Second edition, revised and enlarged. Pp. 341; 470 illustrations. Philadelphia and New York; Lea & Febiger, 1922.

IN the second edition the author has added a description of some of the roentgen-ray machines and tubes now in use for dental work, and has also outlined the principal features of the technic of making intraoral and extraoral films of the teeth and alveolar processes. A little more space given to the dangers of overexposure to the roentgen rays and of high-tension electric currents would have been helpful, especially to beginners.

The bulk of the work is devoted to interpretation, and the numerous illustrations depict very beautifully almost every conceivable abnormality of the hard tissues of the mouth and jaws. Normal roentgenographic studies are shown for comparison. It is particularly emphasized that diagnosis should not depend on the roentgen-ray examination alone; the latter gives evidence, which should be correlated with the history, physical findings, tests and laboratory findings.

The book is to be regarded as a highly reliable source of information to both medical and dental practitioners. It is particularly welcome in view of the almost universal employment of the roentgen ray by dentists, many of the latter having had no training in its use other than that imparted by the dealers.

R. H. I.

---

TUBERCULOSIS AND THE COMMUNITY. By JOHN B. HAWES, 2d, M.D., Director of Clinic for Pulmonary Diseases, and Assistant Visiting Physician, Massachusetts General Hospital, etc. Pp. 168. Philadelphia: Lea & Febiger, 1922.

THIS little volume is a useful addition to the literature which can be utilized as ammunition in campaigns against tuberculosis. A chapter on the cost of tuberculosis compares the public money

spent for prevention and the economic wastage entailed by this disease, and the discussion here is unusually full and frank. In discussing hospitals and sanatoria the analysis is conservative and reasonable. The discussion as a rule steers clear of any question of detail in the treatment of the individual patient and adheres faithfully to the main theme of community problems. There is a chapter on tuberculosis and the nurse (by Miss Billings), and an excellent one on the careless and incorrigible consumptive.

This book should be of interest to physician and layman alike, to the teacher in the public school and to the employer of industrial labor. There is much information contained in its relatively few pages.

R. G. T.

---

THE PRACTICE OF MEDICINE. By A. A. STEVENS, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania, Philadelphia; Professor of Therapeutics and Clinical Medicine in the Woman's Medical College of Pennsylvania. Pp. 1106; 35 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

THE appearance of a new text-book on medicine would naturally make one think that the subject of "medicine" would be presented in a form somewhat different from that followed without exception by all medical text-books. One would anticipate, as an excuse for bringing out a new work, that at least it would be a book which did not follow the regular form instituted years ago but which would present the subject-matter in a modern manner. On the contrary, the reviewer was doomed to disappointment when he went over the book. The usual structure was followed throughout. Thus the first section dealt with infectious diseases, the next with the intoxications and so, on terminating with the diseases of the nervous system. The diseases in themselves are under the accustomed and expected subheads: Definition, Etiology, Morbid Anatomy, Symptoms, Diagnosis, Prognosis, Treatment. It is difficult to understand just why there should be any particular demand for a book such as this which in no way differs from the usual medical text-book type and of which numerous examples exist. When the reviewer picked up the book he hoped that on account of the long and extensive clinical experience of the author perhaps the subject-matter would be presented as a Mackenzie might present it, with much attention paid to the development of symptoms to the functional disturbances that arise secondarily to disease and to the other similar expressions of bodily disorders upon which much stress is now being laid; but such was not the case. Favorable comment on the book would include the statement that it is up to date. Recently described diseases have been reported and an epitome

at least has been presented of the newer studies of diseases with which we have been acquainted for many years. Unfortunately the references are incomplete and would be valueless unless the prospective seeker for more complete information would go to a considerable amount of trouble to get the correct references. Large numbers of prescriptions are also given. Here it is a question if these are of any real value. In only exceptional cases would the same ingredients and exact proportions in which the prescription is written by an author be given to the expectant patient.

---

ORGANS OF INTERNAL SECRETION. By IVO GEIKIE COBB, M.D., M.R.C.S., Neurologist, Ministry of Pensions. Third edition. Pp. 352. New York: William Wood & Co., 1921.

THE third edition of Cobb's treatise on the glands of internal secretion is somewhat altered from that of the previous edition by the addition of three new chapters; the bulk of the text, however, remains the same. In going over this book one is struck with the lack of critical study, the general tendency to draw conclusions from insufficient data and the absence of clinical control. The first portion of the book is rational and well presented, but of the latter part of the book the same cannot be said. It seems a pity to recommend to the practitioner, and this book is dedicated to the general practitioner, the idea that "machine-gun" polyglandular preparations should be given for so many and so diverse conditions.

J. H. M., JR.

MANAGEMENT OF THE SICK INFANT. By LANGLEY PORTER, M.D., Professor of Clinical Pediatrics in the University of California Medical School and WILLIAM E. CARTER, M.D., Assistant in Pediatrics and Chief of Out-Patient Department in the University of California Medical School. Pp. 654; 54 illustrations. St. Louis: C. V. Mosby Company, 1922.

THIS book is unique in that it deals exclusively with the peculiarities of disease as it occurs in infants. In the first part of the volume symptoms are discussed. There are ten chapters here dealing with such symptoms as vomiting, diarrhea, constipation, hemorrhage, fever, pain etc. Treatment is also mentioned in these chapters. In part two, various diseases are taken up in an orderly manner. Thus one finds under the different headings and in separate chapters diseases of the respiratory tract, diseases of the digestive tract and diseases of the heart and circulation. Also in this section there are chapters on diseases of

the blood and lymphatics, diseases of the nervous system, skin diseases, genito-urinary diseases, diseases of the osseous system, internal secretions and infectious diseases. It is the third part of the book, that will cause it to assume an important place in the pediatricist's library. Here, in a most clear-cut and concise manner, are described a great many procedures which are of use in the diagnosis and treatment of diseases in infancy. Intravenous injection, intraperitoneal injection, determination of coagulation time, ventricular puncture, temperature taking, gastric lavage and Schick testing are only some of the things mentioned. Even the cistern puncture of Ayer has found a place in the numerous list. Different formulas and recipes are clearly given and also there is a list of drugs and combination of drugs which may be used in the treatment of diseased conditions. The illustrations are good and to the point. This book should prove of great value to the pediatricist and anyone dealing with sick children. A. G. M.

---

CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE, PEKING, CHINA. By HENRY S. HOUGHTON, Director. Vol. I. Pp. 335, N. p., 1921.

THE establishment of a new center of medical research is in itself a matter of world importance; but when this center is in the oldest and yet—medically speaking at least—the most backward civilization in the world and when its personnel and materiel prove themselves capable of a yearly output of worthy original work that requires 335 pages for presentation, then there is double matter for congratulation. Volume I of the *Contributions from the Peking Union Medical College* is a welcome and important addition to that steadily growing group of similar publications issuing from the active research institutions of this country. Their usefulness in a working library has already been commented upon in this journal. May they long continue to flourish and expand!

It is interesting to note that of the twenty-nine articles comprising the Peking volume, nine are on topics in the domain of parasitology and four of hygiene; while anatomy, bacteriology, chemistry, medicine, surgery, ophthalmology, neurology and the history of medicine are represented by one or two papers each. Sixteen of these articles appeared in the *China Medical Journal*. There is also given a list of eighty-nine publications by members of the staff prior to the compilation of this volume. Although distinctions may be invidious in a publication of such a high average level, one cannot refrain from a word of special commendation on Maxwell's article on "Filariasis in China" and Cowdry's two delightful glimpses into Chinese medical history. Congratulations on the first fruits of

this important center of medical education and research that has arisen in the Far East are distinctly in order, and Volume II, which is apparently well under way, will be awaited with lively anticipation.

E. B. K..

---

MANUAL OF PHYSIOLOGY. By H. WILLOUGHBY LYLE, M.D., F.R.C.S., (Eng.), Examiner in Physiology of the Royal College of Surgeons of England. Pp. 747; 139 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

THIS manual was written to give the student a book of medium size which would at the same time be fairly comprehensive. The author had sixteen years' experience as lecturer at King's College, and the present volume embodies the substance of the lectures delivered there. The book is written in a simple, interesting style, and the author is careful to select his phraseology to make clear his meaning. It may be that, at times, his explanations are too simple and transparent, but this is certainly a pedagogic advantage. On the other hand, there are omissions of some topics which should be at least mentioned in a modern physiology. The figures are mostly of gross and microscopic anatomy, with a small number of tracings. The plan of the book is well suited to the average student, and will give him at least one view or theory in fields where the larger books present evidence for several. W. H. F. A.

---

PRACTICAL INFANT FEEDING. By LEWIS WEBB HILL, Junior Assistant Physician to the Children's Hospital, Boston, and Assistant in Pediatrics, Harvard Medical School. Pp. 483; 32 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

DR. HILL states that he has tried to write a book which will help practitioners, not only to treat but to understand feeding cases as they occur in his daily practice. This is a laudable aim, because unless there is some knowledge of the underlying principles of physiology and metabolism the mere application of methods of procedure will not be successful in the care of either the well or the sick baby. Throughout the volume the results of scientific investigation which have been of practical importance have been mentioned and applied to practice. The literature has been quite extensively reviewed in the chapter on the physiology and pathology of digestion and nutrition. The second chapter is on the stools in infancy and the next two on human milk and breast feeding. A discussion of the history of modern artificial infant feeding occupies a chapter.



Following this are chapters dealing respectively with cow's milk, modification of cow's milk, special preparations, artificial feeding of the normal infant, digestive and nutritional disturbances in the bottle-fed, idiosyncrasy to cow's milk and the diarrheal diseases. In the feeding of the normal infant four periods are considered: From birth to three weeks; from three weeks to nine months; from nine months to one year; the second year. Foods other than milk are advised at nine months, but not before, and these foods are cereals, beef juice, broths, rice and zwieback. Dr. Hill does not believe that vegetables are necessary in the first year of life. While it is stated that many babies may be fed successfully with whole-milk mixtures from birth, arguments are put forward against their use, and mixtures with a higher fat percentage and a lower protein percentage than would obtain in whole-milk dilutions are recommended until the ninth month of life. The indigestions are simply classified as those due to fat, carbohydrate and protein, and the diarrheas into mechanical, fermentative and infectious. Several chapters consider special subjects, such as constipation, prematurity, rickets, pyloric stenosis, and so on.

A. G. M.

— — — — —

**AIDS TO ORGANOTHERAPY.** By IVO GEIKIE COBB, M.D., M.R.C.S., Neurologist, Minister of Pensions. Pp. 183. New York. William Wood & Company, 1922.

THIS small volume of Cobb's is largely an abridgment of his larger volume which is reviewed in the present number of the JOURNAL. It is prepared as a student's aid.

J. H. M., Jr.

**THE WRITING OF MEDICAL PAPERS.** By MAUD H. MELLISH, Editor of the Mayo Clinic Publications. Pp. 157. Philadelphia and London: W. B. Saunders Company, 1922.

A very large number of physicians some time or another in their career attempt to write papers on medical subjects. Many of them do not know how properly to prepare the manuscript for the publishers, and it is for them that this small book is written, as it deals chiefly with how to prepare manuscripts. It also gives some very useful hints on the subject-matter of the hypothetical paper. To one who comes in contact with numerous manuscripts and knows the difficulties under which editors labor this book cannot be too highly recommended. It would be a wonderful assistance to editors if it were in the hands of every medical man who attempts to write.

J. H. M., Jr.

ANATOMY OF THE BRAIN AND SPINAL CORD. By J. RYLAND WHITAKER, B.A., M.B. (Lond.), Lecturer on Anatomy, Surgeons' Hall, Edinburgh. Fifth edition. Pp. 262; 103 figures. Chicago: Chicago Medical Book Co., 1921.

THIS is a book which has been found useful by many medical students in attaining their first knowledge of the structure of the central nervous system. The subject is treated mainly from the standpoint of gross anatomy. The method used is to present everything in the form of diagrams and to use colors liberally in differentiating the various structures. While this may not give a picture true to nature, it certainly makes a very definite impression on the reader, even the dullest. The illustrations of gross structures are clear and well-executed, and excel those of the cross-sections of the brainstem, which are shown in an extremely diagrammatic manner. There are short directions for dissection, but no methods are given for making microscopic sections. W. H. F. A.

---

PROTEINS AND THE THEORY OF COLLOIDAL BEHAVIOR. By JACQUES LOEB. The Rockefeller Institute for Medical Research. First edition. Pp. 292; 4 illustrations, 76 curves. New York: McGraw-Hill Book Company, 1922.

THOSE who have followed Jacques Loeb's interesting investigations in colloidal chemistry will welcome his book which presents a systematic review of his work. The book is distinctly argumentative in nature. The author aims to prove two things: First, that protein chemistry is not essentially different from that of crystalloids, and that the laws of stoichiometry are as applicable to the one as to the other; secondly, that Donnan's theory of membrane equilibrium (which states that the unequal concentration of crystalloid ions on opposite sides of a membrane resulting from the unequal distribution of diffusible ions when one non-diffusible ion is present gives rise to potential differences and osmotic forces) offers the best explanation both quantitatively and mathematically for the physical phenomena of colloidal solutions. In clearing his way to these newer theories, the author takes pains to point out the erroneous deductions, such as Freundlich's adsorption formula, Pauli's hydration theory, and the Hofmeister ion series, that were drawn from experimental results in which the fundamental factor (the hydrogen-ion concentration) had not been given proper consideration. The author presents his subject in an aggressive, interesting manner, using numerous simple experiments to illustrate or prove his point. At times one feels, however, that the discussion is unnecessarily protracted, and that certain portions could be considerably condensed without sacrificing clearness. A. J. Q.

A LABORATORY MANUAL FOR COMPARATIVE VERTEBRATE ANATOMY.  
By LIBBIE H. HYMAN, Ph.D., Department of Zoölogy, University  
of Chicago. Pp. 380; 69 illustrations. Chicago: The Univer-  
sity of Chicago Press, 1922.

THIS is a companion volume to the laboratory manual for elementary zoölogy previously reviewed in this journal (1920, 159, 133). The course in comparative anatomy is very important to students preparing for medicine, and this manual gives directions which will serve as a standard. In the student's career in anatomy there is usually a gap between his pre-medical and his medical work, so that he does not carry over into the medical school the knowledge he has acquired in his college courses. And consequently, while he has a great deal of information, he is not able to make proper use of it. A contributing factor to this state of affairs is that while the human anatomist and the comparative anatomist may be experts, each in his own field, they are not usually masters of both branches. In consequence, the teacher of one branch makes but casual reference to the other field. Such a book as this, if carefully followed and studied, will clarify the student's vision and help to guide him through the intricacies of human anatomy. The subject is treated on the comparative plan: One system at a time is studied in a series of animals, such as a fish, amphibian, reptile and mammal. In all, seven systems or groups of organs are considered, in addition to the external features. Of these, the circulatory system and the endoskeleton are described at the greatest length. The descriptions have been written from the specimens while the dissections were being made, and show the greatest attention to detail. A short account of the development and evolution of each system is included with its description, and constitutes a useful feature of the book.

W. H. F. A.

OBSTETRICAL NURSING. By CAROLYN CONANT VAN BLARCOM, R.N., formerly, Assistant Superintendent and Instructor in Obstetrical Nursing, Johns Hopkins Hospital Training School for Nurses. Pp. 546; 208 illustrations. New York: The Macmillan Company, 1922.

IN contradistinction to the average text-book on obstetrical nursing, which so often describes only the personal ideas of the author and the technic of his particular maternity hospital in a rather narrow manner, the volume at hand by Miss Van Blarcom is offered after an extensive survey and study of the methods and measures used in various maternity centers. There is gained thereby for the text a wider outlook and a broader scope than is

usually found. The principles of obstetrical nursing are presented in a pleasing and comprehensive manner. The addition of the forms, rules and directions for care of obstetric patients used by several public health associations should enhance the value of the book to the community nurse or visiting nursing aide.

The illustrations are excellent; many are from well-executed photographs and supplement the text in a graphic manner. The chapter on nutrition of the mother and baby is an innovation in such a book. The scientific side of the question seems to have been too greatly stressed for the average nurse. P. F. W.

THE PRACTICE OF MEDICINE IN THE TROPICS. Edited by W. BYAM, O.B.E., Lecturer on Tropical Medicine at St. George's Hospital Medical School and R. G. ARCHIBALD, D.S.O., Director, Wellcome Tropical Research Laboratories, Sudan Government, Gordon College, Khartoum. Volume I. Pp. 856; 334 illustrations. London: Henry Frowde, Hodder & Stoughton, 1921.

THE first volume of a very portentous reference text-book contains almost entirely what might be called the preliminary phases of tropical medicine; that is to say, it is composed of sections on hygiene and minor sanitation, on nursing in the tropics, on entomology, on laboratory methods, on snakes and snake poisoning, and on toxicology. All these various sections are most complete and well presented. The section on sanitation, for example, contains nearly two hundred pages; it seems to be very well executed. The section on laboratory methods is also carefully compiled: One portion of it, on transfusion of blood, is a copy of the method used in the American army during the war and published by the American Red Cross in France. If the subsequent volumes of this work are as carefully gotten up as the first volume, then, to the English-speaking profession, there has been presented a notable work and one which will offer to the physician practising in the tropics or subtropics a treatise on the diseases indigenous to those climates which will be unsurpassed in the English Language.

J. H. M., JR.

A TREATISE ON GLAUCOMA. BY ROBERT HENRY ELLIOTT, M.D., B.S., Sc.D., F.R.S.C., late Superintendent of the Government Ophthalmic Hospital, Madras; Ophthalmic Surgeon to the Seamen's Hospital Society. Second edition. Pp. 650; 213 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

THE early chapters of this book are devoted to the subject of the secretion of the intraocular fluid and its excretion from the

eye under normal and abnormal conditions. A review of the experimental work so far done on the problems of the intraocular pressure follows. The author very fairly presents the views of other workers in this field and very frankly expresses his own views upon the problems still under discussion.

The latter part of the book is devoted to the pathology of glaucoma and medicinal and operative treatment of glaucomatous eyes. As is to be expected, the sclerocorneal trephine operation is presented in detail and the various other operative procedures for glaucoma are hardly given the space to which they are entitled. The book is well arranged and—even for the reader who is not convinced that the trephine operation is the final answer for the problem of glaucoma—is most valuable and enjoyable.

B. F. B., JR.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**Quinine in Cardiac Disease.**—R. SINGER and H. WINTERBERG (*Wien. Arch. f. inn. Med.*, 1921, 8, 329) report, from Wenekebach's Clinic, results obtained from the extensive use of quinine in cardiovascular conditions. The salts used are the dihydrochloride carbamide of quinine and the bimuriate of quinine. On normal subjects the administration of 2 or 3 grams of quinine in divided doses produces almost constantly a generalized sense of warmth, occasionally dizziness and tinnitus and frequently the bitter quinine taste in the mouth. The physiologic action consists of a moderate acceleration of the pulse and an almost complete disappearance of sinus arrhythmia; there are minor alterations in the form of the electrocardiogram and an increase in rate in cases of sinus bradycardia. The physiologic action in a general way is similar to that of atropine. In "irritable heart" there is a tendency toward improvement in the general condition of the patient and in subjective symptoms. The drug was found of especial value in treatment of precocious systoles, particularly of such as were of ventricular origin and not associated with obvious cardiac disease. Both oral and intravenous routes of administration were found satisfactory. Striking results were obtained in cases of paroxysmal tachycardia treated with 0.5 gm. of quinine sulphate intravenously. After prolonged administration by mouth of small doses of quinine, a reduction was observed in the rate of the auricular waves in a case of flutter. Suggestive results were obtained in instances of hypertension and Cheyne-Stokes respiration. Quinidin is suggested as preferable for use in precocious systoles, flutter and fibrillation of the auricles. Quinine is suggested as a drug to be tried intravenously for obstinate paroxysmal tachycardia that has resisted the simpler methods of approach.

**Effect of Hepatic Extract on the Cardiovascular Apparatus.**—ROGER (*Presse méd.*, May 24, 1922) reports experimental studies with hepatic extracts which follow a series of observations upon the effect of extracts of various organs upon the heart and cardiovascular apparatus. In the case of hepatic extracts he finds two groups of chemical substances grouped according to their physiologic action. Some are alcohol-soluble and exert a striking vasoconstrictor action. Among the other substances is one that exerts a powerful effect upon the heart, producing a bradycardia of sinus origin. One tracing shows a pulse-rate of less than one-third the normal rate, which followed the injection of hepatic extract into an experimental animal.

---

**A Ten Year Old Strain of Fibroblasts.**—EBELING (*Jour. Exp. Med.*, 1922, 35, 657) describes a strain of fibroblasts obtained from the heart of a chick embryo which has completed the tenth year of its life *in vitro*, during which time it has passed through 1860 generations. The author believes that fibroblasts will proliferate indefinitely, as do colonies of infusoria. During this time the technic of preserving this "potential immortality" has been progressively perfected, and more than 30,000 cultures have been derived from the original fragment. With the development of methods whereby differences of less than 10 per cent in the rate of growth could be detected, these cultures have been used for physiological studies by Carrel, Ebeling, and others. The cells remained indefinitely young or grew old according to the food material which they were given and the extent of the elimination of their catabolic substances. Thus embryonic juice was found to contain a substance which increases the velocity of cell multiplication to a high degree. In the same manner, it was found that adult serum produces an effect opposite to that of embryonic juice. This inhibiting power of a serum increased very much with the age of the animal from which it was obtained. It was also shown that the strain responds to the presence of a foreign protein in the culture medium by becoming immunized against its action. As it has become possible lately to obtain strains of lymphocytes and of epithelial cells living *in vitro* by practically the same procedure that is used for fibroblasts, the scope of these studies will be increased. Several excellent photomicrographs of the proliferating fibroblasts accompany the article.

---

**Studies on Asthma.**—LARSON, PADDOCK and ALEXANDER (*Jour. Immunol.*, 1922, 7, 81) report their observations of bronchial asthma and allied conditions. The work was carried on in the asthma clinic of the Bellevue Hospital, New York City. It embraced the following investigations: (a) A continued study of the clinical considerations of asthma, (b) observations on skin reactions, and (c) effects of vaccine therapy. Briefly from the clinical standpoint the authors emphasize the importance of recognizing bronchial asthma as speedily as possible, eliminating those cases which fall into an entirely different group. They classify their cases as follows: (1) Bronchial asthma, simple and uncomplicated; (2) chronic bronchial infection with its complications simulating bronchial asthma; (3) bronchial asthma, complicated by chronic bronchitis. The first type is very well defined by a typical history suggesting a sensitiveness to a foreign protein. The second type is quite the opposite.

There is no history of allergic conditions. There is a bronchial infection simulating bronchial asthma. The third type is primarily type one, on which infection is superimposed. The immunological studies reveal several important facts. The authors compare the different methods of performing the skin tests. They feel that the intracutaneous method of determining an individual's sensitiveness is far more accurate than the scratch method. In the first place if one is using dry preparations with the scratch method there is no way in which to tell whether they have lost their potency. With solutions, contaminations are easily detected. To compare the two methods a number of known sensitive individuals were tested by the cutaneous and intracutaneous procedures with the same solutions. The experiment reveals that certain individuals, whose asthma is brought on by a specific pollen, fail to react by the scratch method but with an intracutaneous injection a very definite skin reaction occurs. The authors further state that the reaction depends somewhat on the length of the scratch. A long scratch for example gives a broader reaction than a short one. They also are of the opinion that the location of the scratch influences the reaction although they offer no explanation why this should affect it. The reaction is also influenced by the amount of protein brought in contact with the cells, and the amount of solution injected into the skin. With reference to vaccine therapy in asthma, the authors are rather optimistic. They feel that in asthma associated with bronchial infection vaccines, if given with caution, are worth a trial. How these agents act has not been determined, and further study is planned.

**Neurorecurrences Following Arsphenamine.**—ZIMMERMAN (*Arch. Dermat. and Syph.*, 1922, 5, 723) reports a study of 39 cases of neurorecurrences (precocious neurosyphilis) following arsphenamine. The material is in large part from the syphilis department of the Johns Hopkins Hospital. He divides the cases into three groups: (1) Acute syphilitic meningitis with or without focal cranial nerve lesions; (2) meningitis of moderate or slight intensity, manifested chiefly by headache and focal lesions; (3) a group in which there are no general symptoms of syphilitic meningitis, the entire complaint being due to a focal lesion. He demonstrates that the facial and auditory nerves are those most frequently involved (in 18 cases), both nerves frequently being involved in the same patient. The clinical details of the author's cases are well summed up in a most exhaustive table. From a study of the literature two groups of neurorecurrences may be differentiated from the pathological standpoint: First, a diffuse meningovascular process, and second, focal lesions involving especially the optic, auditory and facial nerves, without diffuse changes. The first group always presents definite abnormalities in the cytobiology of the cerebrospinal fluid, whereas in the second, the fluid is often normal. Neurorecurrences are to be explained on the basis of resumed activity of temporarily suppressed organisms in a host unable to develop resistance owing to therapeutic interference. The importance of a thorough course of mercury in all cases of early syphilis is emphasized. According to the author, efficient mercurial treatment, administered immediately following arsphenamine, eliminates these serious reactions on the part of the central nervous system as successfully as combined therapy.



The treatment of these cases is briefly discussed. The success of therapy depends, according to the author, almost altogether on how soon treatment can be begun after the onset of neurological symptoms.

**Endamœba Dysenteriae in Hodgkin's Disease.**—KEFOID and SWEZY (*Jour. Am. Med. Assn.*, 1922, 78, 1604) report a case which clinically and pathologically resembled Hodgkin's disease. In the enlarged glands of this patient the authors found cells which they regard as amœba, probably *Endamœba dysenteriae*. They base this interpretation on the structure of the nucleus of this cell, particularly as it appeared during mitosis. The most important evidence adduced is the numerical contrast between the number of chromosomes believed to be normal for human cells and the number observed in the abnormal cells. The latter number corresponds to that observed in amebas. The authors suggest the possibility of Hodgkin's disease being amœbiasis of the lymphatic system.

**Amœbiasis of the Bones.**—KEFOID and SWEZY (*Jour. Am. Med. Assn.*, 1922, 78, 1602), on similar grounds to those described above, believe that certain ameboid cells found in the bone-marrow in cases of arthritis deformans are true amebas, and they suggest the inference that the organism may be the etiologic factor in Ely's second or non-bacterial type of arthritis deformans.

## SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

**Decapsulation of the Kidneys in Bright's Disease.**—SANDERSON-WELLS (*British Med. Jour.*, December 3, 1921, p. 940) says Edebohl's principles were attacked by physiologists upon these grounds: That the renal arteries are end-arteries and terminal; that the blood supply from the capsule is insignificant; that renal tissue once destroyed does not regenerate; and that chronic nephritis is the local expression of a general disease and a cure must remove the cause. Experimental work upon animals showed that a new capsule was formed in a few weeks thicker and denser than the normal capsule; that there were fewer vessels in the new than in the old. Injections were made into the renal arteries and the aorta with the renal arteries tied. The general opinion as to the result of these experiments was that there was but slight communication. Stursburg, however, found on injecting into the aorta with the renal artery tied that the injection penetrated even to the papillæ. Although the outlook appears disappointing from physiological and pathological aspects, the clinical case reports are excellent.

The uremic patient has been restored to consciousness, while suppression of urine and edema disappear. Patients apparently doomed have returned to work; many have subsequently been pronounced cured by high authorities. The operation therefore deserves consideration under two conditions: First, as an emergency in eclampsia, uremia and suppression of urine; the more desperate the extremity the more certainly it should be discussed; and second, in chronic cases when medical treatment has failed after a thorough trial. In both the above classes the heart and arteries should be reasonably sound, which probably means that most success will be obtained in the first half of life.

---

**The Surgeon as a Pathologist.**—BOND (*British Med. Jour.*, December, 1921, p. 973) says that a capacity to elaborate a substance or substances closely allied to, if not identical with, glycogen is possessed by leukocytes, myelocytes, and certain epithelial cells. In the case of the white blood cells, this capacity is in the main limited to the polymorpholeukocytes when they emigrate or escape from the blood stream. In the emigrated leukocyte this glycogenic substance takes the form of a colloid liquid which is rapidly exuded from the cell and gives a delicate mauve color with iodine. In the myeloid cells of the red marrow and in some myeloma cells this substance is also present and is somewhat evanescent. In certain epithelial cells of the mucous membranes which line the orifices of the digestive, respiratory and genito-urinary canals this iodophil substance is present in a more granular and less soluble form. It is more closely incorporated with the cell cytoplasm and stains a red or red-brown color with iodine. The same or an allied substance is also constantly found in certain cancer cells of epithelial origin. In the primary growth it is present in the cells which form the cell nests. In common with the irregular growth of the epithelial cells in the cancer area the disposition of the iodophil cells also undergoes a change. These are reduced in number and are collected in irregular groups rather than in stratified layers. This iodophil substance is also present in the epithelial cancer cells found in the lymph glands and in other secondary deposits. The presence of this capacity for elaborating iodophil substances by cancer cells in secondary deposits is an indication of the retention of some degree of original function by these cells in their abnormal situation and is associated with important problems of cell heredity.

---

**The Treatment of Gastric Ulcer.**—MOYNIHAN (*British Med. Jour.*, February 11, 1922, p. 267) says that medical treatment if properly carried out for a sufficiently prolonged period, should enable an ulcer to heal. The need for surgical treatment is a confession that such treatment is unattainable or has failed. The procedures that have been adopted are as follows: Gastroenterostomy; excision of the ulcer; gastroenterostomy combined with excision; gastroenterostomy combined with destruction of the ulcer by cautery (D. C. Balfour's operation); median resection of the stomach (sleeve resection); gastroenterostomy combined with jejunostomy; and partial gastrectomy. This last operation has been most satisfactory for the author. In gastrectomy the mortality in his hands has been 2 per cent. The quality of recovery is excellent. Secondary operation was necessary only once in a series of ten years' duration. There has only been one

unsatisfactory result in this group of 118 cases, a young woman from whom the author removed the stomach for chronic ulceration of the lesser curvature. A group of tuberculous mesenteric lymph nodes were also taken out. Since operation intermittent attacks of diarrhea have occurred with temporary wasting. In none has there been the development of carcinoma or a return of ulceration.

**Epididymitis and Suprapubic Prostatectomy.**—WHITE (*Lancet*, February 18, 1922, p. 321) says that inflammatory changes in the epididymis as a result of prostatectomy are the rule, for 82 per cent of cases studied gave this result. Five degrees of inflammation were recognized ranging from mere thickening of the epididymis to pus formation involving the adjoining testicle in slough. The inflammation may be unilateral or bilateral. It is generally more advanced in one side than the other. The amount of sepsis in the prostatic cavity is a very important point in determining the degree of epididymitis, for the prostatic cavity is cup shaped with very imperfect drainage. Moreover the torn ends of the ejaculatory ducts in the posterior wall of the cavity are continuously in contact with infected material.

**Aberrant Adenoid Cystic Epitheliomas.**—JOHNSTON (*Ann. Surg.*, 1922, 75, 331) says that adenoid cystic epitheliomas of the salivary gland type occurring in the tissues of the mouth and face are not as uncommon as the literature would indicate. Such neoplasms have been reported but not properly recognized and histologically interpreted. The tendency is to regard them as sarcomas. To this fact may be attributed some startling surgical cures. The characteristic tumor has slight malignant properties. Therefore it does not ulcerate and invade in its early stage. Radium treatment has been entirely successful in these cases.

**Pathology of Lung Suppuration.**—ASCHNER (*Ann. Surg.*, 1922, 75, 321) says that lung suppurations may be divided into bronchiectasis, a general disease of the bronchi in one or more lobes (bronchiectatic abscess is a localized suppurative process in the course of a bronchus and thus far observed only in post-tonsillectomy cases), suppurative pneumonia, a diffuse purulent process. Certain interesting histological changes have been observed: metaplasia in bronchial epithelium; epithelial lining of bronchiectatic abscess and proliferation of smaller bronchioles and air passages resembling proliferation of bile passages in portal cirrhosis.

**The Influence upon Toxicity and Trypanocidal Activity of Shaking Acid and Alkalinized Solutions of Arsphenamine and Solutions of Neoarsphenamine in Air.**—SCHAMBERG, KOLMER and RAIZISS (*Am. Jour. Syph.*, 1922, 2, 1) say that the undue shaking of alkalinized solution of arsphenamine increases the toxicity; the shaking of such solutions is rarely necessary. The shaking of acid solutions of arsphenamine for one minute beyond the time necessary to effect solution is accompanied by a slight increase in toxicity. Ten minutes' extra shaking increases the toxicity still further. The shaking of solutions of neoarsphenamin for even such short periods as one minute is accompanied by a great increase in toxicity. Shaking for ten minutes enormously

increases the toxicity. It would appear from the studies of Roth and from those which the authors have conducted that neoarsphenamine should be dissolved with as little agitation and exposure to air as possible. The trypanocidal power of acid solutions of arsphenamine is considerably increased after one minute of shaking but is decreased after ten minutes' shaking. The trypanocidal power of alkaline solutions of arsphenamine is considerably increased at the end of one minute's shaking and the increase is still evident after ten minutes' shaking. The explanation of the increase in trypanocidal power is probably to be found in the formation of arsenoxide, which is known to exert a greater trypanocidal and spirocheticidal effect than arsphenamine. The shaking of solutions of neoarsphenamine is not accompanied by increase in trypanocidal effect.

---

**Resection of the Lungs for Suppurative Infections.**—LILIENTHAL (*Ann. Surg.*, 1922, 75, 257) says that chronic pulmonary suppurations wholly or partially of the bronchiectatic type are rarely curable without the extirpation of the pathological focus. The surgical removal of a single pulmonary lobe for chronic pus infection has a mortality of about 42 per cent. The danger is much greater when more than one lobe is infected or in the presence of other complications. Remissions of weeks or even months may occur spontaneously. Palliative operations may be followed by improvement, rarely by apparent cures. The commonest cause of the disease is infection due to aspiration of infected material during tonsillectomy. Radial operation should not be undertaken short of several months after the onset unless the disease is obviously spreading.

---

**Malignancy in Exstrophy of the Bladder.**—SCHOLL (*Ann. Surg.*, 1922, 75, 365) says that exstrophied bladders that are subject to constant irritation and trauma have an extensive glandular covering, the result either of metaplasia from the normal covering or of hyperplasia of glands in the mucosa. Such glandular structure often shows characteristics approximating malignancy. In nine cases of exstrophied bladder in which material for histologic study was available, two were definitely malignant and two showed a typical cellular formation varying markedly from the normal. In the reported cases of malignancy of exstrophied bladders which are relatively frequent the growths were adenocarcinomas. This glandular malignancy is the type that would develop from irritation and hyperplasia of glandular structures.

---

**Sarcoma of the Long Bones.**—MEYERDING (*Surg., Gynec. and Obst.*, 1922, 34, 321) says that 35 per cent of the patients were inoperable or refused operation. In many instances, undoubtedly early diagnosis would have given the patients a chance for a cure. Thirty-two of the 35 patients who died had amputations. The most malignant sarcomata were the osteosarcomata. Eight of these patients lived seven months after operation on the average. Ten patients have died who had excision and cautery. Five died of pulmonary metastasis. The principal points to be decided before operating are malignancy, metastasis, and the extent of bone involved. With early diagnosis, with care to exclude patients with metastasis, and with the use of radium and Coley's toxin, prolongation of life may be looked for following operation.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**Congenital Obstruction of the Duodenum.**—SCHRODER (*Jour. Am. Med. Assn.*, 1922, 78, 1039) reports a case in which this condition existed. He says that the most confusing thing is the differential diagnosis from pyloric stenosis. Forceful vomiting, gastric peristaltic waves, the presence in the stomach of the entire previous feeding, and absence of milk stools occur in both conditions. Bile in the vomitus may be absent in duodenal obstruction if the obstruction is above the duct as usually happens. A mass may be felt in both conditions, the dilated and hypertrophied muscle in the ring and wall giving the sensation to the palpating hand. The author had this experience as did others who have reported this condition. If the precaution is taken of using the barium meal and the fluoroscope to supplement the clinical findings, an early diagnosis becomes possible, and operation may save some of these infants. Up to the present there seem to be only two successful operations on record, one in a child of eight weeks and the other in one ten days old. An early gastroenterostomy is the operation of choice, although one of the successful cases on record was cured by a duodenoenteroanastomosis, which is the ideal operation if it is possible to use it. The fixation of the duodenum makes it a difficult proceeding. In the case here reported the diagnosis could not be made from the external inspection at the time of the first operation, which was performed upon the diagnosis of pyloric stenosis. Later after fluoroscopic studies a jejunostomy was done, and would have been of great benefit in an older child. There was probably leakage from the wound as the cause of the poor result. It seems probable that had the diagnosis been made at the time of the first operation the chance for success with a gastrojejunostomy would have been fair.

**Chronic Arthropathy.**—HYMAN and HERRICK (*Jour. Am. Med. Assn.*, 1922, 78, 1043) report a case in an infant of twenty-eight months in which the most striking thing on examination was the marked thickening of all the long bones, and the clubbing of the fingers and toes. In this child congenital syphilis was ruled out by the absence of any suggestive family or past history, by two negative Wassermann tests, and by the absence of any clinical evidence of syphilis. Rickets did not seem to be a reasonable explanation of the extensive thickening of the shafts of the long bones when the epiphyses did not give the appearance of the epiphyses in rickets. The roentgenograms were similar in many respects to those seen in infantile scurvy, particularly in the suggestion of Trümmer's zone at the lower end of the tibiae. This disease could not explain the clubbed fingers and toes, and the bone changes of the metacarpals and distal phalanges as seen in this child. Careful review of the history did not reveal anything suggestive of scurvy during the

first twenty-two months of life, and after that time the diet had been under careful supervision. It seems likely that the line of increased density just above the epiphysis of the lower end of each tibia was due to some metabolic disturbance other than scurvy. It was extremely interesting to note that the periosteal thickening in the phalanges and metacarpal bones took place during the last four months of observation.

---

**The School Child before and after Tonsil and Adenoid Removal.**—DAVIS (*Jour. Am. Med. Assn.*, 1922, 78, 1187) divided the children to be studied into two main groups: Group I comprised about 6000 children from six, twelve or fourteen years of age, and Group II included about 1500 children from twelve to eighteen years of age. From each of these groups were taken the children with enlarged tonsils and adenoids, and the children who had been operated on for removal of these structures. Only markedly enlarged or obstructing tonsils and those usually termed diseased tonsils were included. Local causes of poor breathing, such as deviated septum, enlarged turbinates, polyps and the like, were eliminated as much as possible, and all were given the same routine examination. About 5 per cent of the total number of children had been operated on for the removal of tonsils in each group. In Group I there were recorded 450 pronounced tonsil and adenoid cases, or about 7.5 per cent of the total number examined. One hundred, or 22 per cent of this number, had enlarged cervical glands and 9, or 2 per cent had cardiac murmurs at the apex. All the children with enlarged adenoids were bad breathers. In this group there were 296 children who had had their tonsils and adenoids removed with breathing good in 132, or 44 per cent; fair in 67, or 22 per cent; and poor in 97, or 34 per cent. Of these 296 children 114, or 38 per cent, had enlarged cervical lymph glands, and 10, or 3.5 per cent, had apical cardiac murmurs. A large number of the children had varying degrees of gland tissue proliferation in the pharynx and about the tonsil spaces. Some gave undoubted signs of syphilis. Some were asthmatic and subject to recurrent bronchitis and irritation of the upper respiratory tracts, and others were eczematous. In Group II, 21 children were referred for operations. This is about 1.5 per cent as compared with 7.5 per cent in the other group. Twenty per cent of these had enlarged cervical glands, and none showed heart murmurs. Of the 93 children in this group whose tonsils had been removed, breathing was good in 57, or 62 per cent; fair in 19, or 20 per cent; and poor in 17, or 18 per cent. While 34 per cent of the younger children who had removals breathed poorly, the older group showed only 18 per cent. This was probably due to the older children having reached a stage of immunity to infections, and also to the increasing size of the air space with dehydration and cessation of growth of lymphatic tissue. Twenty-five per cent of the children of this group had enlarged cervical glands, and there were 5 cases of heart disease, or 5.3 per cent. The incidence of heart disease is really very low.

---

**The Clinical Findings in the Normal Chest of the Child.**—AUSTRIAN, LANDIS and BLACKFAN (*Report of the Committee on Medical Research, Natl. Tuberculosis Assn.*, May 6, 1922) state that the data obtained on percussion and auscultation of the lungs of normal children show wide variations from a fixed standard. These variations are usual and are

considered to be within normal limits. Inasmuch as these changes are dependent upon alterations that persist as the remains of past infections of the respiratory tract, it is obvious that a careful history with special reference to all infections is necessary if diagnostic errors are to be avoided. Even careful histories must be considered with judgment, as minor infections are soon forgotten by many, and among the less intelligent even more significant illnesses are not recalled. Failure properly to evaluate these deviations from a fixed standard often lead to unwarranted diagnosis of disease and even less justifiable treatment. With a proper appreciation of the widest variations that the normal may present the informed clinician can better understand the findings of the roentgenologist, and each coöperating with the other is less liable to error. D'Espine's sign as indicative of enlarged tracheo-bronchial lymph nodes is of little value. Recognition of and familiarity with these data is of cardinal and practical importance to every patient. Without a proper appreciation of these facts no intelligent differentiation between a normal and an abnormal respiratory tract can be made.

---

**The Use of the Carbon Arc Light in the Prevention and Cure of Rickets.**—HESS and UNGER (*Jour. Am. Med. Assn.*, 1922, 78, 1596) experienced that in the winter, and especially in the early spring, rickets develops on every diet. It is generally mild and overlooked, but if routine clinical, roentgenological, and chemical examinations are carried out, it is surprising what a small proportion of bottle-fed infants will be found to have escaped rickets by March or April. They have also found that rickets is not limited to the artificially fed infant. A recent survey of breast-fed infants showed that by the end of March about one-half showed definite roentgenological evidence of rickets. The infants that they treated by the carbon arc light had been on standard diets, including raw certified milk, dry milk, malt soup and protein milk. All received orange juice daily. Huldsehinsky and others had used the mercury vapor quartz lamp for this purpose. The rays which this lamp emits are rich in ultraviolet, but its spectrum differs markedly from that of the sun, in that it is discontinuous, and that much of its ultraviolet rays are of wave lengths considerably shorter than those of the sun. For these reasons it was deemed worth while to try the effect of the white flame carbon arc lamp, which more nearly approaches the sun's spectrum. The fact that this lamp is very rich in luminous rays was another reason for testing its therapeutic value, for it seemed that it might provide illumination at the same time as therapy. The infants entirely naked were placed at a distance varying from three to nine feet from the lamp, and were provided with spectacles or other covering for the eyes. This form of irradiation does not lead to any tanning of the skin. This shows that pigmentation is not an essential factor in heliotherapy of rickets. In every instance there was a subsidence of the rickets, which was evident by roentgen ray often after daily exposures for only two weeks. This consisted in calcification of the lower epiphyses of the radius and the ulnar, which increased progressively as the treatment was continued. Accompanying these changes there was the constant increase in the inorganic phosphate of the blood, which in some cases had a tendency to fall after heliotherapy was discontinued. The carbon arc lamp was found in the laboratory

as well as in the clinic to be a very effective agent in the prevention and cure of rickets. It is comparatively inexpensive, and its rays are not irritating to the skin, so that it can be used for hours with perfect safety. The use of the lamp has the advantage over heliotherapy in that it can be used in the winter months when the tendency toward the development of rickets is the greatest, and when it is not possible to apply heliotherapy on account of the impossibility of exposing the body of the child to the direct rays of the sun at this season of the year.

---

**The X-ray Findings in the Normal Chest of the Child.**—PANCOAST, DUNHAM and BAETJER (*Report of the Committee on Medical Research, Natl. Tuberculosis Assn.*, May 6, 1922) found that the normal chest of the child is subject to such wide variations from the roentgenologic point of view as to be beyond the possibility of exact description. The conglomerate shadow, commonly called the hilum shadow, when found lying entirely within the inner third or zone of the lung can be entirely disregarded, or regarded as normal except where it is made up of a solid mass of homogeneous shadow, showing undoubted evidence that it represents a growth or mediastinal pleurisy. Calcified nodes at the root of the lung, without evidence of lung disease, are of no significance except as possible evidence of some healed inflammatory condition, possibly but not necessarily tuberculosis. They are a common finding in the normal chest. In the normal lung the bronchial trunk shadows are not visible in the extreme apical regions. For convenience of description the remainder of the lung is divided into three vertical zones, extending outward from the lateral border of the spinal shadow to the lateral chest wall. The inner zone contains the root shadows. The midzone contains the trunk shadows, gradually fading out into their final subdivisions. The peripheral zone contains radiating lines from these and fading off before the periphery is reached. Where in the midzone or peripheral zone these shadows do not disappear in the characteristic fashion described, the appearance may be evidence of a variety of conditions, past or present, of an inflammatory nature or otherwise. It may accompany a tuberculous process, but is not necessarily indicative of tuberculosis. They feel that the use of such terms as peribronchial tuberculosis and parenchyma tuberculosis should not be used in the interpretation of roentgenograms of the chest. Also they feel that until corroborated by laboratory or clinical findings the use of such terms as active and quiescent should not be definitely applied to evident lesions demonstrated on plates.

---

**The Diagnosis, Prognosis and Early Treatment of Poliomyelitis.**—LOVETT (*Jour. Am. Med. Assn.*, 1922, 78, 1607) points out that it is commonly known that many cases of poliomyelitis are overlooked in the early stages, being incorrectly diagnosed as all sorts of febrile affections, and the diagnosis is usually cleared up only after the paralysis develops. Laboratory diagnosis can be made in the early stages by spinal tapping. The fluid in the acute stages of the disease is clear and colorless, and does not show great increase of pressure. In the first week there is an increase in the cells, due to mononuclear cells of various types, of which the lymphocyte is the most common. The cells may increase to as many as from 1000 to 2000 per cubic millimeter. The



globulin reaction, which is weak at first, increases to its maximum by the end of the third week. The only difficulty in the laboratory diagnosis is between poliomyelitis and tuberculous meningitis. The diagnosis from clinical symptoms is very important as the facilities for laboratory examination are not always available. This cannot be made from the history. Trauma cannot cause this disease. A moderate or high fever occurring suddenly without known cause and accompanied by symptoms in the gastrointestinal or respiratory tracts is suspicious, especially between June and November. The most suspicious symptom of all is stiffness at the back of the neck in attempts to flex the head, but there is nothing really characteristic about the attack. Occasionally the part that will be paralyzed is affected by prickling or numbness. The paralysis may occur in one or two hours or three or four days from the beginning of the attack. After the first few days the diagnosis is very often only too obvious to those who are familiar with the fundamentals of the affection.

---

## OBSTETRICS

---

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

---

**The Results of Cesarean Section from 1911 to 1920 Inclusive.**—HOLLAND has undertaken to collect the records of the hospitals of Great Britain regarding Cesarean section in ten years. His totals are: for contracted pelvis, 33,372; for eclampsia and toxemia, 231; for antipartum hemorrhage, 208; for other conditions, 386. In Cesarean section for contracted pelvis, when the mother was not in labor and therefore no attempt to deliver had been made, the maternal mortality was 11.6 per cent; early in labor, 1.8 per cent; late in labor, 10 per cent; after induction of labor, 14 per cent, and after attempts at delivery, 27 per cent. The fetal mortality of cases where forceps had been tried was 27 per cent and the early mortality of children delivered by section after considerable labor was nearly 11 per cent. As might be expected, peritonitis and sepsis were the principal causes of the mother's death. There were 33 cases of operation through the lower uterine segment: 12 of them were extraperitoneal operations with 4 deaths; 20 transperitoneal operations with 1 death. In 46 cases of Cesarean hysterectomy there were 8 deaths. When these cases are analyzed it is found that the cases were severely complicated before operation. With all possible deduction of hysterectomy the maternal mortality of Cesarean operation in cases not in labor was 1.4 per cent; early in labor, 1.8 per cent; late in labor, 9.4 per cent, and after attempt at delivery, 26.5 per cent. The fetal mortality at the time of operation was 3.9 per cent and later on among these children a mortality of 4.2 per cent; the later the operation is performed in labor the higher the fetal death rate, and when the operation is done after

the forceps has failed the fetal death rate is very high. It is interesting to note that the maternal mortality of abdominal Cesarean section as indiscriminately practised for eclampsia is 32 per cent, and in eclampsia and toxemia fetal mortality is 50 per cent among infants dying at the operation and those surviving. The writer speaks of other toxemias of pregnancy and those causing eclampsia which is to our mind a confusion of terms and ideas. Thus in 29 cases of what he calls the albuminuria of pregnancy, a maternal mortality after Cesarean section was 20 per cent. The statistics would have been more valuable if eclampsia and what he calls other toxemias had been placed under one head. In placenta previa the statistics are somewhat confused; thus he speaks of *complete* and *central* with a mortality of 14 per cent; uncomplicated, etc., with a mortality of 9.3 per cent, and "placenta previa" 18 cases, 1 death. Obviously these statistics are not clear. Among his cases were 5 Cesarean hysterectomies with no mortality. The fetal mortality in these cases was low, 7 per cent at labor. Among the children surviving the operation and remaining for some time in the hospital the mortality was 22.3 per cent. Unquestionably the fetal mortality of placenta previa treated by Cesarean section was comparatively low. On using the term accidental hemorrhage, probably to include accidental separation of the normally implanted placenta, the statement is not clearly defined. In 66 cases treated by Cesarean section the maternal mortality was 27 per cent. It is difficult to imagine what concealed and revealed hemorrhage may be, but this is mentioned together with concealed hemorrhage and 68 cases of accidental hemorrhage. When Cesarean hysterectomy and the ordinary simple Cesarean section are compared, or these cases of hemorrhage, the mortality of the former is four times as great as that of the latter. This may be because these cases were complicated at operation. Eighty-six per cent of the children in these anomalous hemorrhages were lost. In the miscellaneous cases of various types, numbering in all 366, mortality varied in accordance with the severity of the complication for which the operation was done. The paper is interesting and valuable for the large number of cases studied and the painstaking effort made to arrive at the true position of Cesarean section as practised at present in the British Empire.

---

**Galactocoele.**—GRYNFELT and TZÉLÉPOGLOU (*Gynéc. et obst.*, 1922, 5, 222) publish a well-illustrated and comprehensive paper upon this subject. They find that the condition known as galactocoele is not a primary pathological condition. It is a secondary result of various pathological processes in the mammary gland. From the standpoint of anatomy, several varieties may be distinguished. One, the cystic, which arises from the dilatation of the milk ducts; second, the interstitial, which is formed by the excessive secretion retained in the connective tissue around the gland substance; third, the adenogalactocoele, which is an adenocystic tumor containing milk; fourth, the pyogalactocoele, which is a chronic abscess in the milk duct and surrounding tissue. From the standpoint of pathology these conditions may arise in two ways: First, from inflammation, which in accordance with its nature, intensity, location and duration, creates the conditions

necessary for the development of the different varieties; second, from traumatism which ruptures the milk ducts and produces lactorrhagia. In the literature of the subject the most commonly reported is the adenogalactoceles. Very frequently a number of factors enter into the pathological condition present, producing complex anatomical varieties which are called mixed galactoceles. The clinical development in a given case varies with the anatomical type—a point of practical interest deserving further investigation. In all cases the knowledge that a galactocoele may coexist with an adenofibroma explains the hesitation which obstetricians feel in giving a definite prognosis on any line of treatment.

---

**The Treatments of Placenta Previa by Abdominal Hysterotomy.**—BROUHA, of Liège (*Gynéc. et obst.*, 1922, 5, 198) has operated 11 times by Cesarean section for placenta previa. Six of these patients were primiparæ, of whom 4 were operated upon before labor; 1 at the beginning of labor; 1 was at seven months, the remainder at term or very near term. In 1 case complicated by uterine fibroid hysterectomy was performed. Ten of these women recovered, 8 without complications and 2 after some fever. One survived delivery for only four hours. Two of the children died two or three hours after the operation without symptoms, except those of weakness. Of the 2 cases whose recovery was complicated by fever, 1 had infection in the abdominal wound. She was in very bad general health and was operated upon as an emergency without much preparation, but finally made a good recovery. The second patient, recovering with fever, was a young frail primipara, who had a serious hemorrhage at the seventh month, at which time she was placed under the care of a midwife. Hemorrhages occurred at intervals, but were treated by hot douches, containing laudanum. When she was finally examined, it was found that the finger could be carried through the cervix against the placenta, which was central. The examination was followed by profuse hemorrhage, and a tampon was used to check it. As the tampon became soaked, it was replaced and operation was finally done. The patient's convalescence was complicated by fever, although the abdominal wound healed naturally and involution of the uterus proceeded naturally. No evidence could be found of pelvic inflammation. It was thought that an important element in bringing about the cessation of fever was the production of a fixation abscess, which on the twenty-seventh day after operation, obtained a half-pint of pus. The case ending fatally was a primipara, aged thirty-four. She had had some hemorrhage during pregnancy, but when near term was taken with a profuse bleeding which rapidly made her anemic. There was slight dilatation of the cervix, but it remained very hard, with the placenta covering the lower segment. The patient had rallied from the operation, seeming in unusually good condition, when suddenly her pulse became worse and she died from rapid dilatation of the heart. The writer is in favor of Cesarean section for placenta previa in a large proportion of cases.

---

**Hysteropexy and Gestation.**—ROSNER (*Gynéc. et obst.*, 1922, 5, 185) reports the case of a patient aged thirty, the mother of three chil-

dren, who had been operated upon in 1920 for prolapse and retroflexion of the uterus. Anterior and posterior colporrhaphy, a plastic operation on the perineum and hysteropexy, had been performed. About two months after the operation the patient became pregnant, and during the third month of her pregnancy she suffered greatly from pain in the lower part of the abdomen, which pain finally became unendurable. At five months the uterus was very sharply anteverted, the fundus fixed behind the symphysis, and the posterior wall of the uterus distended. The round ligaments could not be made out with bimanual examination. The uterus seemed to be in a sort of sac formed by the edges and tendons of the recti muscles. There was great pain on pressure. On vaginal examination, the cervix was very high up, carried far back; the uterus could not be pushed up by vaginal manipulation. The situation was such that the child could only develop by distending the posterior wall of the uterus, and the patient's suffering was so great that operation was undertaken. On opening the abdomen two adhesions were found which fixed the fundus of the uterus in the neighborhood of the insertion of the round ligaments in the abdominal wall. These adhesions were tense and covered by peritoneum. Without disturbing the uterus these adhesions were severed without much hemorrhage. The points of incision were covered by peritoneum and the abdomen closed. The patient made an uninterrupted recovery, and the uterus developed normally. The patient was examined three times before full term. The uterus grew normally in size; at the tenth month the cervix was in normal position and the head of the child engaged in the pelvic brim. It was not difficult to recognize the fact that the development of the anterior wall of the uterus had been retarded by the fixation operation; while the posterior wall of the uterus had been overdistended. Labor occurred spontaneously at term with slight laceration of the vaginal wall and perineum. The weight of the child was normal, the mother making a good recovery.

---

**Eclampsia Post Partum Apparently Cured by Decapsulation of the Kidneys.**—FEY (*Monatschr. f. Geburtsh.*, 1922, 56, 256) states that he has had good results in the use of drugs in the control of eclamptic patients. In the following case, however, he resorted to operation. The patient was aged thirty-six, and had previously given spontaneous birth to two living female children with an interval of about two years. Seven years later she had an abortion at three months. In the pregnancy under consideration the patient was fairly well in the early months, but as the later months approached she had swelling of the legs, headache and sought medical advice. She entered the hospital and gave spontaneous birth to a living male child. Early on the following morning she had eclamptic convulsions with a very small secretion of dark brown urine, containing albumin, casts and red blood cells. The patient was unconscious and her blood-pressure high. The lower extremities became edematous; the breathing was stertorous; five hours after the first convulsion 250 cc. of blood was taken. As the patient did not essentially improve, she was subjected to decapsulation of both kidneys. The kidneys were found large and hyperemic; the capsule of the kidneys was very firm and tense, and when it was incised there was profuse bleeding, especially from the left kidney, but no protrusion

of kidney substance. When the capsules were stripped back the parenchyma was found to be not pale and anemic, as has been stated by some, but very hyperemic. As there was free bleeding on the left side, a tampon of iodoform gauze was introduced. Convulsions ceased after the operation; consciousness and memory gradually returned; the quantity of urine markedly increased, and albumin and casts almost disappeared. Urinary fistulas developed on both sides but eventually closed. Unfortunately at five weeks the child died of pneumonia and convulsions, but the mother made a good recovery.

---

## PATHOLOGY AND BACTERIOLOGY

---

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

---

**The Erythropoietic Action of Germanium Dioxide.**—Maintaining exact conditions of control, HAMMETT, NOWREY and MÜLLER (*Jour. Exper. Med.*, 1922, 35, 173) injected a sterile 0.4 per cent solution of germanium dioxide into four lots of male and female albino rats. Two lots received in four doses at intervals of four days a total of 6.6 mg. per kilo of body weight and the other two were given 45 mg. in three doses at similar intervals. Weekly determinations of the erythrocyte and leukocyte counts of the blood were made seven days apart. It was found that all of the test rats responded to the germanium dioxide by a marked and sustained rise of from one to nearly five millions in the number of erythrocytes in the blood. Those rats which showed a lower initial count responded better, and *vice versa*. There was no indication that the larger doses of germanium dioxide exerted a greater stimulating effect on the production of the resultant erythrocythemia than the smaller doses. Evidently the effect appeared quickly, the red cell count rising within a week after two injections. The coagulability of the blood became increased while color changes were noted in the liver and bone marrow. In a second communication, HAMMETT and NOWREY (*Jour. Exper. Med.*, 1922, 35, 507) reported the results of a histological comparison of the liver, spleen, bone marrow, circulating young erythrocytes and differential counts in the albino rats receiving germanium dioxide, with their litter controls. It was found that while the livers of the test animals showed a capillary dilatation and engorgement, and the spleens were more congested than in the controls, there was no evidence of red-cell formation in these organs. In the bone marrow, however, there was evidence of a marked stimulation in formation of nucleated erythrocytes, as well as an increase in the young red cells in

the circulating blood. No noteworthy differences in the values for the various types of leukocytes in the circulation, as determined by differential counts, could be found. The authors conclude from their experiments that germanium dioxide is a potent erythropoietic agent and that the source of the erythrocythemia is the increased production of red-cell precursors by the bone marrow.

---

**The Internal Secretion of the Pancreas.**—With the knowledge that since the acinous but not the islet tissue of the pancreas degenerates after ligation of the pancreatic ducts, and assuming that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland, BANTING and BEST (*Jour. Lab. and Clin. Med.*, 1922, 7, 25), working in conjunction with J. J. R. MACLEOD, have conducted certain experiments on dogs in an attempt to prepare an active extract of the island of Langerhans. The pancreatic ducts were ligated for ten weeks, to allow complete degeneration of the acinous tissue, after which interval the degenerated pancreas was quickly removed under chloroform anesthesia and the extract prepared by slicing into a chilled mortar containing Ringer's solution and partially freezing the tissue. The half-frozen gland was then macerated and filtered, and the filtrate, now at body temperature, was injected into eight to sixteen month old dogs depancreatized by the Hédon method or at the initial operation. The results of various experiments on six dogs are shown in detail with the aid of charts. Over seventy-five doses of extract from degenerated pancreatic tissue have been administered to ten different diabetic animals. It was found that intravenous injections of the extract invariably reduced the percentage of sugar of the blood and the amount of sugar excreted in the urine, the extent and duration of the reduction varying directly with the quantity of the extract injected. Rectal injections were not effective and pancreatic juice destroyed the active principle of the extract and boiled extract produced no effect on the reduction of blood sugar. Extracts made 0.1 per cent acid were effectual, however, in lowering the blood sugar, and extracts prepared in neutral saline and kept in cold storage remained potent for at least seven days. The presence of the extract enabled a diabetic animal to retain a much greater percentage of injected sugar than it would otherwise. That the reducing action was not a dilution phenomenon was indicated by the fact that the hemoglobin estimations before and after injections of the extract were the same, that administration of large amounts of saline did not effect the blood sugar and that similar quantities of extracts of other tissue did not cause the reduction of blood sugar. The authors are convinced that the extract contains the internal secretion of the pancreas, which is the factor operative in controlling carbohydrate metabolism; but they feel that the results of their "experimental work," which certainly appear to mark an epoch in our understanding of diabetes mellitus, "as reported in this paper, do not at present justify the therapeutic administration of degenerated gland extracts to cases in the clinic."

---

**The Diagnosis of Syphilis in Malarial Subjects by the Wassermann Reaction.**—JOHNSON (*Jour. Path. and Bacteriol.*, 1921, 24, 145) reported the results of 738 complement-fixation tests for syphilis on 74 cases of

malaria, all of which were under treatment with quinine (20 to 30 grains daily). The tests consisted of the original Wassermann (using two M. H. D. of complement), Tschernogobow's modification, Fleming's modification and the Hecht-Fleming method. In 19 cases the first blood specimen was collected during an actual rigor or at a short interval after a rigor, in 45 there was no record of rigor but the first specimen was obtained when the parasites were found in peripheral blood and in 10 cases the blood was collected when no parasites were found but typical relapses subsequently developed with parasites in the finger blood. All cases clinically syphilis or giving a history of previous syphilitic infection were excluded. On retesting the bloods only 7 per cent were found to give positive Wassermann reactions. These investigations indicate that the blood in active benign tertian, malignant subtertian and mixed malaria does not give a positive Wassermann reaction; that positive findings are due to syphilitic infection or to certain factors in the technic employed or to non-specific changes in the patient's serum; that in such cases the serum should be retested and that a positive reaction confirmed by a subsequent test is evidence of luetic infection.

---

**The Wassermann Reaction in Relapsing Fever.**—Out of 18 cases of relapsing fever, ROAF (*British Jour. Exper. Path.*, 1922, 3, 59) found 11 positive to the Wassermann reaction (Emery's and Fleming's modifications) at some stage of the disease, but 6 of the 7 negative cases were tested only once. Excluding 2 of the positive cases in which the test was not repeated, 3 out of 9 persisted during the period of observation (seventeen to twenty days), while all others had become negative eight to thirteen days after the onset of the fever. Two cases were negative on first examination, but became positive three and six days after onset. As a result of these observations the author believes that a transient positive Wassermann reaction may be found as a constant phenomenon during the acute stage of relapsing fever; that the transient character distinguishes it from the reaction due to syphilis, and if the positive result persists in a given case, syphilis may be suspected also.

---

**Digestion of the Esophagus as a Cause of Postoperative and Other Forms of Hematemesis.**—PRINGLE, STEWART and TEACHER (*Jour. Path. and Bacteriol.*, 1921 24, 396) call attention to the fact that, in all probability, many of the cases interpreted as postmortem digestion of the esophagus have, in reality, an origin during life and report 18 cases, 16 of which were fatal. Ten of the cases were surgical in nature, 2 were associated with accidents and 6 with medical diseases. The outstanding clinical feature was vomiting of black or brown material, twenty-four to thirty-six hours before death, this symptom being found on 13 occasions. In the esophagus itself two striking and distinctive phenomena consist in the presence of black sloughs indicative of intense congestion and hemorrhage and the contrast between the broken-down esophagus and the stomach, which is either totally free from digestion or only slightly digested. Two of the cases showed a slight involvement, 7 presented extensive ulcerations and 9 had perforated with widespread destruction of the lower portion of the esophagus. Hemorrhages are always present in the esophageal wall and sometimes in the lungs and pleuræ. Microscopically the condition is a severe ulceration

attended by necrosis, solution of tissue and an acute inflammatory reaction. The authors believe that the condition is not rare, that it is not an agonal manifestation, "but one the nature of which can be diagnosed during life and which might be amenable to treatment."

---

## HYGIENE AND PUBLIC HEALTH

---

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

---

**Typhus Fever on the San Juan Indian Reservation, 1920 and 1921.**—ARMSTRONG (*Public Health Reports*, 1922, 37, 685) reports on an outbreak which resulted in 63 cases and 27 deaths on an Indian Reservation in the arid Southwest. The epidemic occurred among an Indian population showing 90 to 100 per cent infestation with head and body lice. The infection was probably introduced by laborers from Mexico. The early cases were variously diagnosed as influenza, measles and typhoid fever. The infection existed for about six months before being recognized. The problems of control were made more difficult by the isolation of the affected region, poor roads and scarcity of fuel and water. Delousing was accomplished by the application of a mixture of kerosene and gasoline, the use of a solution of nicotine, 1 : 1000, and by steam and boiling in the case of fomites. An emulsion of kerosene 2 parts, soap 1 part, and water 4 parts was also used to advantage for the body and hair. Cases were in general isolated in their own homes.

**Experimental Studies on Tuberculous Infection.**—KRAUSE (*Am. Rev. Tuberc.*, 1922, 6, 1) confirms his belief in the Cohnheim-Cornet-Ribbert Law of Localization, in view of a constantly recurring demonstration provided by infection of a culture of low virulence known as R. 1. Krause emphasizes his belief that at its culmination every case of tuberculosis represents, in some degree, the fruition of a long sequence of accidental circumstances. Krause has made a careful study of the course of tubercle bacilli from the path of entry to the lungs in guinea-pigs and rabbits. He has shown that in the guinea-pig the tracheo-bronchial nodes show gross tubercle earlier than the lungs. In rabbits, on the other hand, he generally finds marked involvement of the lungs with slight or only moderate infection of the tracheo-bronchial nodes. Between the microscopic structure of the normal lungs of guinea-pigs and rabbits, there are important differences, which would permit tubercle bacilli to pass through the lungs of the guinea-pigs on to the



trachco-bronchial nodes, but would tend to retain them in the lungs of the rabbit. Krause states that while the bloodvessels are potent factors in the spread of infection, they act merely as conveyers of bacilli. The real site of the pathologic development of tubercle would appear to be in the lymphatic system, in accordance with the view of Calmette. From mucous membrane the bacillus makes its way into the lymphatic system; and from plugged capillary it does likewise. Where it will focalize is determined largely by lymphatic anatomy (and, therefore, lymphatic physiology); and variations in lymphatic anatomy will determine differences in focalization. Krause has shown that fundamental anatomical differences are actualities which give point to Tendeloo's views of tuberculous focalization, based on physiological inquiries; though he is not inclined to follow Tendeloo all the way, and especially not in regard to non-continuous infection against the lymph stream. With this experimental evidence, he asks a few questions which continually recur to him but which thus far he has not had time or opportunity to investigate in the thorough way which their solution would require. Does human tuberculous infection normally tend to the lung root in early life because then lymphatic drainage is more active and intrapulmonary channels more open and unobstructed than later? In other words, is the child's lung more comparable to that of the guinea-pig, which may be looked upon as constituting one type? With increasing age, do human lungs undergo internal changes which bring them nearer to the type which is normal for rabbits? Does there normally occur an increase and development of intrapulmonary lymphoid tissue over a few years, or through many years? Do formerly open lymphatic paths thus become more or less obstructed, so that bacillary retention within the lung is favored? How much do the inhalation of foreign bodies and the repeated occurrence of respiratory infections alter the puerile lymphatic structure which was once normal? Gardner and Willis have shown that in guinea-pigs the intrapulmonary lymphoid tissues proliferates markedly in response to the irritation of dusts, and that these overdeveloped masses then remain as permanently enlarged structures in the lymphatic paths. Miller has described and figured the same occurrence in man. Dust which is not cast out by the ciliated epithelium comes to be laid down in human lungs along the lymphatics. With increasing age fibroses mark our lungs in varying degree. How much have all these processes to do with bringing about anatomical changes which will tend to arrest bacilli in their lymphatic passage to the nodes and to fix them in the lung itself? Is it not remarkable that even when the adult human lung has massive tuberculosis, the root nodes participate relatively little in the process? Here we have a companion piece to what is normal for the rabbit. What has blocked the relatively easy passage to root which characterizes childhood infection? Krause thinks it is not wholly improbable that the several parts of the lung may differ in details of finer lymphatic structure—in details not fundamental perhaps, yet decisive as regards fixation of bacilli—throughout life or perhaps only at certain periods. May the apical occurrence of localized adult tuberculosis, which is due to relatively slight infection, dependent on such factors? Do we lose our general tendency to lymphatic tuberculosis as we grow older, because with increasing age our lymphatic flow becomes less active and our lymph nodes more .

impermeable? A rising incidence of renal and epididymal tuberculosis suggests that age brings no diminution of blood-borne metastases; but wherever the lymphatic apparatus may be conceived as entering into the spread of infection, there is in general much less tuberculosis as childhood passes into adolescence, adolescence to full maturity and completed growth to old age. Krause leaves all these as questions, as phases of a much larger problem, which, he submits, is worthy of attack from the point of departure which he has tried to establish. This is that the determinants of tuberculous infection are almost innumerable; yet among them there exists a very fundamental one which will always bulk large in the shaping of the final result and is comprised in the fact that a varying and variable anatomical structure establishes the loci of infection and to a great extent the further development and progression of infection from these.

---

**Relation of Faulty Cultures to Diphtheria Mortality.**—O'KEEFE (*Boston Med. and Surg. Jour.*, 1922, 186, 603) states that immediately following the common use of diphtheria antitoxin, and after the more general use of bacteriologic diagnosis, the mortality curve of diphtheria took a marked downward trend. As the value of antitoxin became more widely recognized by the profession and public, this curve went lower still. Carey states that in the first decade of the last twenty years the death rate of this disease fell from 43 per 100,000 to 15 and a fraction. He goes on to state that there has, however, been a fairly constant mortality rate during the latter ten years of this twenty-year period. With the advent of toxin-antitoxin administration it is not unreasonable to expect, in the near future, still further lowering of the diphtheria death rate. O'Keefe concludes from his observations that one of the factors in delay of diagnosis of diphtheria is the failure to recognize that unless cultures are properly taken laboratory diagnosis will not be reliable. No amount of care or skill on the part of the bacteriologist can compensate for faulty technic on the part of the practitioner in securing a fair sample of the organisms existing in the membrane or exudate concerned. Twenty-four to forty-eight hours' delay in the administration of antitoxin frequently results, owing to reliance placed upon faultily taken cultures.

---

**Tularemia Francis 1921, Six Cases of Tularemia Occurring in Laboratory Workers.**—LAKE and FRANCIS (*Public Health Reports*, 1922, 37, 392) report on 6 cases of laboratory infection occurring in laboratory workers. Their paper is summarized as follows: All of the persons (6) who have been intimately engaged in the past two years in the laboratory in handling or dissecting rodents infected with the Utah strains of tularensis have suffered an attack of tularemia. The diagnosis in each of the 6 cases rests upon the occurrence of a febrile period lasting about three weeks, positive serum reactions for agglutination and complement-fixation to antigens composed of *Bacterium tularensis* and the absence of febrile attacks in 100 other persons in the laboratory coming in casual contact with infected rodents. Consideration must be given to the skin of the hands as a possible portal of entry of the infection in laboratory workers even in the absence of local lesion or lymphatic

denitis. A second attack has recently occurred in Case I of the above series, two years and five months after his first attack. The second attack was associated with evident cracks on the fingers, on one of which there developed an inflammatory papule which was soon followed enlarged, painful and tender lymph nodes in the epitrochlear and axillary regions of the corresponding side, but without fever or other constitutional disturbance. *Bacterium tularensis* was isolated from the papule by guinea-pig inoculation. The absence of constitutional symptoms in the second attack, although there was a local lesion and consequent lymphadenitis, is accounted for by the persistence of immune bodies acquired by the first attack. Unrecognized cases of tularemia probably occur in the known foci of infection in the United States, some of which may have febrile attacks without local lesions, while some may have local lesions and a secondary regional lymphadenitis without very notable constitutional disturbance. Routine serological tests for agglutination especially and for complement-fixation, using antigens composed of *Bacterium tularensis*, would probably not only detect cases in known foci of infection but would bring to light unknown foci. Positive serological reactions are known to persist for two years after an attack. Light might be thrown upon the etiology of some fevers of undetermined origin. A warning is sounded against unwarranted indifference to an infection which in our experience has claimed all of those who have persistently worked with it in the laboratory.

---

**The Serological Grouping of Meningococcus Strains Isolated in New York City in 1921 and 1922.**—EVANS (*Public Health Reports*, 1922, 37, 1247) has studied the immunological relations of meningococci isolated from recent cases of meningitis and compared them with strains which prevailed a few years ago. It is shown that, judged by bacteriotropin reactions, there has been a marked shifting of grouping, with a tendency to increase among the unclassified strains.

---

**The Delinquent.**—LESLIE (*Public Health Reports*, 1922, 37, 1297) calls attention to the great economic loss and suffering entailed by delinquents who become public charges in penal institutions. Work of certain American observers is reviewed and commented on. A plea is made for study of the situation and for reshaping of the policy of the community in dealing with mentally deficient actual and potential criminals. The public-health bearings are especially brought out in connection with prostitution and venereal disease.

---

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only with the distinct understanding that they are contributed exclusively to this JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

OCTOBER, 1922

---

ORIGINAL ARTICLES.

CLINICAL OBSERVATIONS ON BLOCK OF THE BRANCHES  
OF THE AURICULOVENTRICULAR BUNDLE.

BY JAMES B. HERRICK, M.D.,

AND

FRED M. SMITH, M.D.,

CHICAGO.

THIS report is based on clinical observations that were made on thirty-five patients in each of whom the probable diagnosis of bundle branch block was made from the electrocardiogram. The QRS group was atypical in each of the three leads and exceeded 0.1 second in duration. Some of these patients came under observation during the time that studies<sup>1 2</sup> were being made on experimental lesions of the branches of the auriculoventricular bundle of the dog, so that in this clinical study it was natural to attempt to correlate as nearly as possible the electrocardiographic findings with those produced experimentally in the dog.

*Age Incidence.* Twelve patients were in the fifth and 13 in the sixth decade of life; 6 were under fifty and 4 above seventy; 20 were between fifty-five and sixty-five years. The youngest patient was twenty-three years old.

*Possible Etiological Factors.* In 17 there was an associated chronic nephritis. Five had arterial hypertension with negative urinary findings. The blood Wassermann test was made in 10. In five of these the reaction was positive. Each of these gave a history of having had a chancre. It was noted that the age incidence in these 5 was below fifty years. Ten gave histories of having

had inflammatory rheumatism. Five had been addicted to alcohol and 2 had had typhoid fever.

*Symptoms.* Eighteen were short of breath on slight exertion. Seventeen had difficult breathing even when at rest. In 8 the duration of the shortness of breath had existed for more than two years, in 10 more than one year and in the remaining 17 less than one year. Twelve had cardiac asthma. Ten gave histories of having anginal pain. In 4 of these the pain had at one time been very severe, lasting several hours, and morphin was required for relief. Twenty had noticed swelling of the feet.

*Physical Findings.* In every instance the cardiac dulness was increased to the left. Twenty-five had an apical systolic murmur. Ten had a systolic murmur over the aortic area. Only one had the diastolic murmur of aortic regurgitation. This patient had a distinct widening of the aorta. Twelve had gallop rhythm. A muffled first tone was a common finding. Twenty had rales in the bases of the lungs, a palpable liver and some edema of the ankles. Twenty-three had a systolic blood-pressure ranging from 175 to 250. In eight of these a *pulsus alternans* was noted. Seventeen had albumin and granular and hyaline casts in the urine.

*Clinical Course Since First Seen by Us.* We have been able to follow 21 of these patients. Twelve died within eighteen months after the first examination. The average duration of life was less than one year. Ten died from cardiac failure. One of these died suddenly following recovery from a prostatectomy, presumably a coronary accident. Another after a cataract operation died from a thrombosis of the cerebral arteries. The youngest patient of the series died on the same day after the resection of the left fifth rib for an adhesive pericarditis. The clinical diagnosis of extensive cardiac hypertrophy, adhesive pericarditis, double mitral lesion, tricuspid regurgitation, fibrous myocarditis and cirrhosis of the liver was verified by necropsy. Autopsies were done in 2 other cases in which an extensive sclerosis of the coronary arteries and a disseminated myocardial fibrosis were found. In neither case was the conduction system examined histologically. Six of the 10 patients that are known to be alive are in bad condition. Two of them have had major operations. Following the operations they had very stormy periods of cardiac upset. Since recovery the clinical manifestations of cardiac weakness have rapidly progressed. Four patients have reported that they were improved.

*Electrocardiographic Findings.* The prevailing ventricular phases were broad at the base and notched or slurred near or at the apex. The duration of the *QRS* group in all instances exceeded 0.1 second and in many the duration approached 0.15 second. The *T*-wave assumed a direction opposite to that of the most prominent ventricular deflection. In thirty-two instances the chief ventricular wave (Fig. 1, top) was positive in lead I and negative in lead III.

In the remaining three the *S*-wave was the most prominent wave in lead I and the *R*-wave in lead III (Fig. 1, bottom).

The fiber of the galvanometer was standardized so that 3 millvts. caused a deflection of 30 mm. In 12 the amplitude of both the *R*

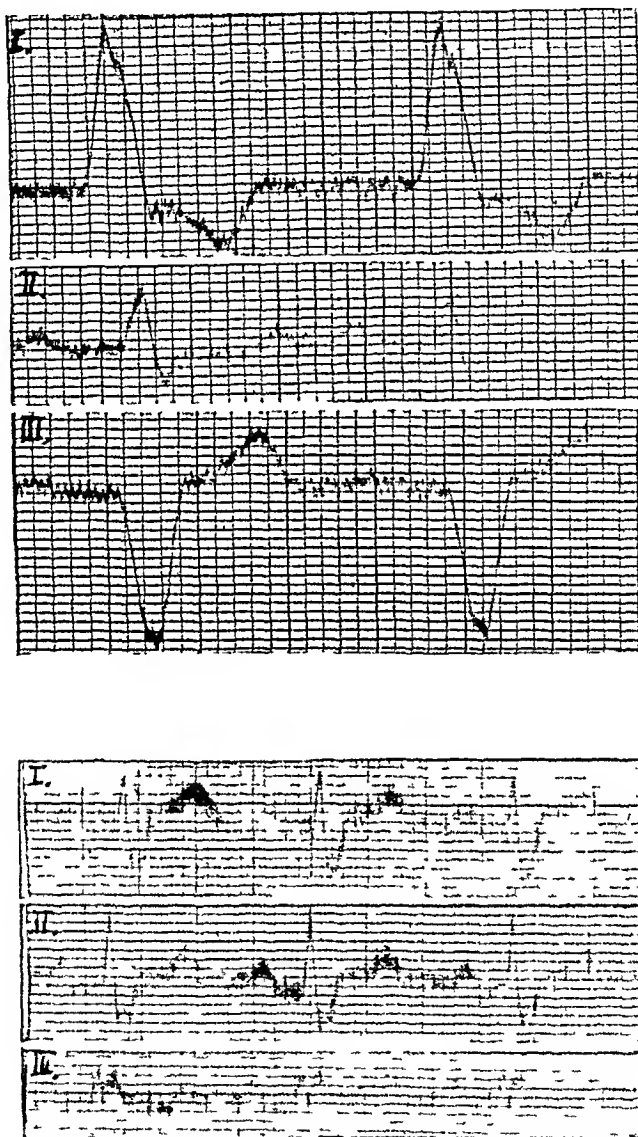


FIG. 1.—*Top:* The prevailing ventricular phase is positive in leads I and II and negative in III; it is blunt or slurred at the apex, and its duration is about 0.14 second. *Bottom:* The chief ventricular deflection is negative in lead I and positive in lead III. The duration of the *QRS* group is about 0.12 second.

and the *S* deflections was large and in 10 small. In 3 the amplitude of the low deflection curves increased while the patients were under observation. One of these patients has been studied over a period of one year. During this time electrocardiograms have been taken at frequent intervals. When first seen he was orthopneic, had

passive congestion of the lungs, engorgement of the liver and edema of the ankles. He had a systolic murmur at the apex and a gallop rhythm. The systolic blood-pressure was 238 and the diastolic 120. There was a *pulsus alternans*. He was kept in the hospital until the heart improved and afterward rested at home four months. The initial electrocardiogram (Fig. 2) shows very atypical broad *R* and *S* deflections of low amplitude. In

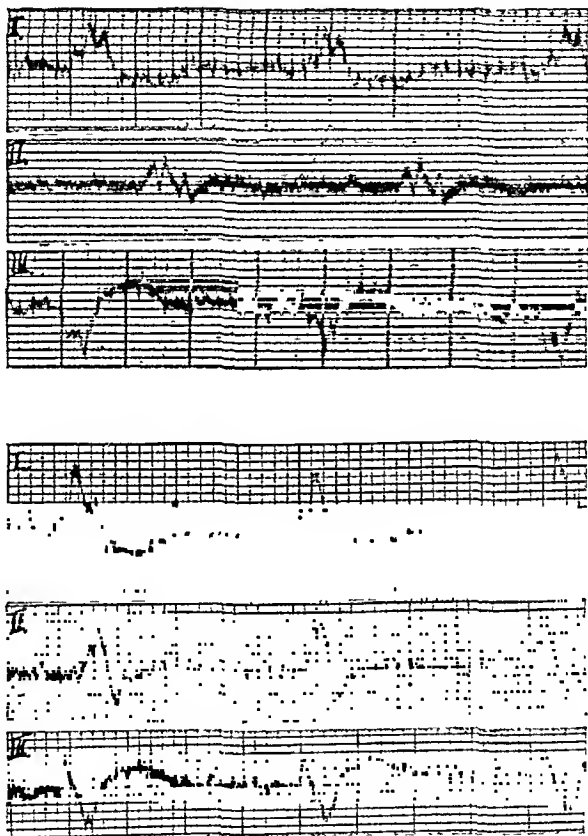


FIG. 2.—*Top:* Initial electrocardiogram taken December 20, 1919. *Bottom:* This electrocardiogram was taken January 5, 1920. The patient had been at rest in bed for two weeks.

the later electrocardiograms (Figs. 2, 3, 4) the *R* and *S* waves become less atypical and their amplitude gradually increases. In the last record (Fig. 4) the prevailing ventricular deflection is tall and resembles that of a left ventricular preponderance. The duration of the *QRS* group is, however, still prolonged. This change in the electrocardiogram was coincident with the clinical improvement of the patient. He was relatively free from cardiac symptoms for three months, and during that time worked as a

pressor. Later he became short of breath again and the amplitude of the ventricular deflections decreased. He is at present in the hospital in a critical condition. The electrocardiogram now is similar to that when first seen.

The electrocardiogram (Fig. 5) in one case showed some *QRS* groups that approached the normal in duration. We were able

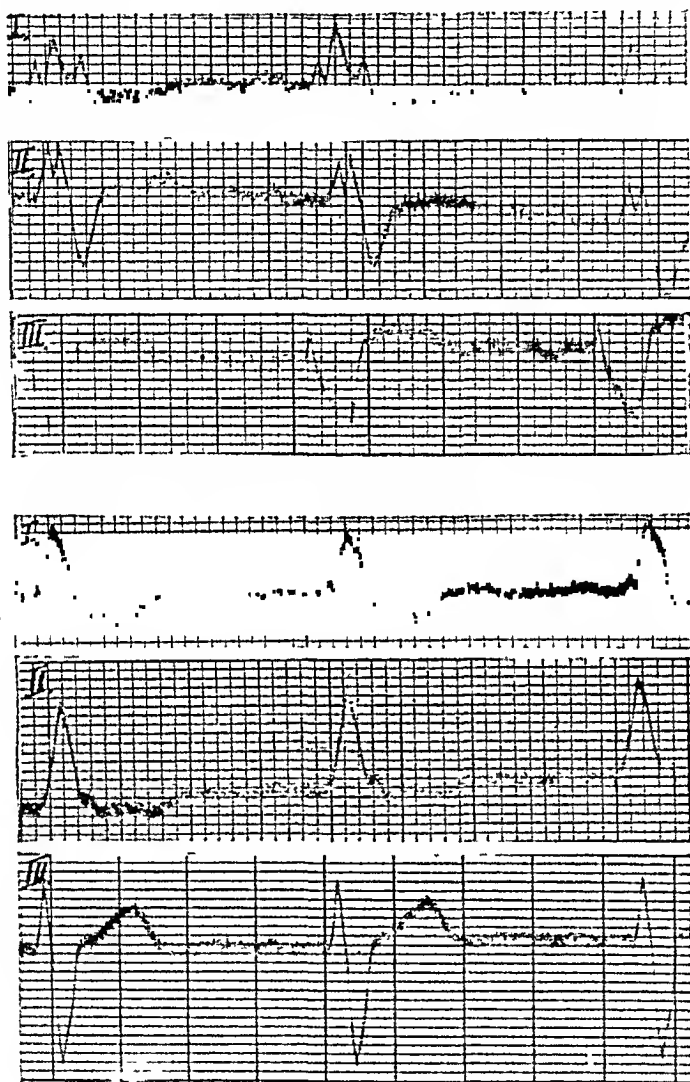


FIG. 3.—*Top*: Electrocardiogram taken April 14, 1920. *Bottom*: Electrocardiogram taken June 21, 1920.

to follow this case, and the *R*-waves of leads I and II were later apparently normal in duration, while the *S*-wave in lead III was slightly broad (Fig. 5, bottom). When first seen at the cardiac clinic of the Central Free Dispensary this patient was in an extremely bad condition. She was cyanotic and very dyspneic. The heart-rate was about 120 per minute and the auricles were fibrillating.



The electrocardiogram taken at this time is shown in Fig. 5 (upper tracings). She returned to the clinic two weeks later. She was then markedly improved. The heart-rate was about 65 per minute and she could walk fairly comfortably. The electrocardiogram shown in Fig. 5, (lower) was taken at this time.

Three patients produced electrocardiograms in which the *PR* interval was slightly more than 0.2 second. Three had heart-block. In one of these the partial block of the main stem was transient (Fig. 6). In leads I and III there is seen a 2-1 auriculo-ventricular ratio. In lead II all the sinus impulses are passing over the bundle. The transmission period is, however, prolonged.

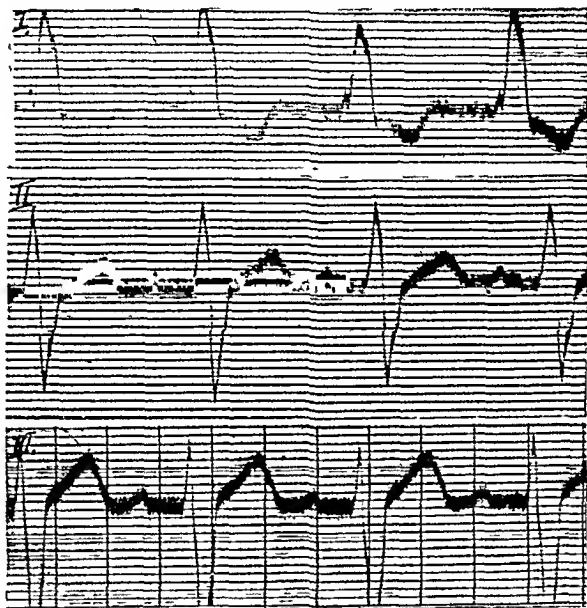


FIG. 4.—This record was made in October, 1920. The chief ventricular deflection is now tall and less atypical.

This patient had many attacks of Adams-Stokes syndrome and died suddenly from cardiac failure about six months following the time this electrocardiogram was taken.

In 5 instances there were auricular fibrillations.

**Comment.** All the patients of this series had symptoms and physical findings indicative of cardiac weakness. In 17 (48.5 per cent) these manifestations of weakness were very marked. That the outlook is poor is shown by the clinical course following the first examination. Eleven (52.3 per cent) of the 21 whose subsequent history was followed died within eighteen months, the average duration of life being less than one year. This mortality is in accord with the figures of other observers. Willis<sup>3</sup>

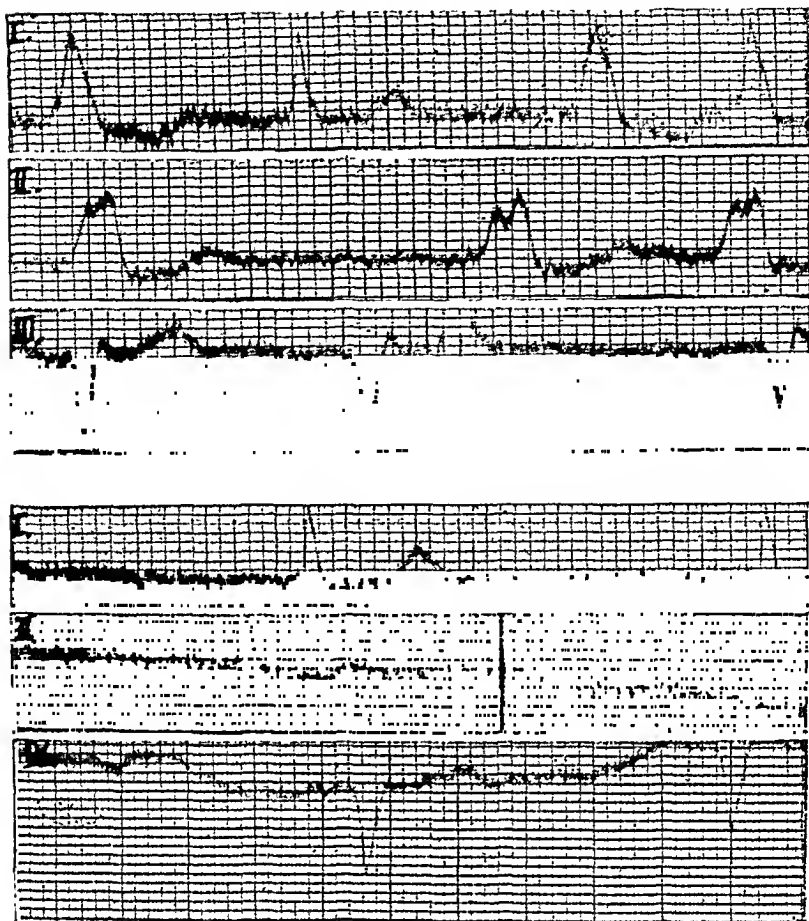


FIG. 5.—*Top*: Initial electrocardiogram; a few of the prevailing ventricular phases have an approximately normal duration; the others are very atypical and have a duration of about 0.15 second. *Bottom*: This electrocardiogram was taken two weeks later. The clinical condition of the patient was markedly improved.

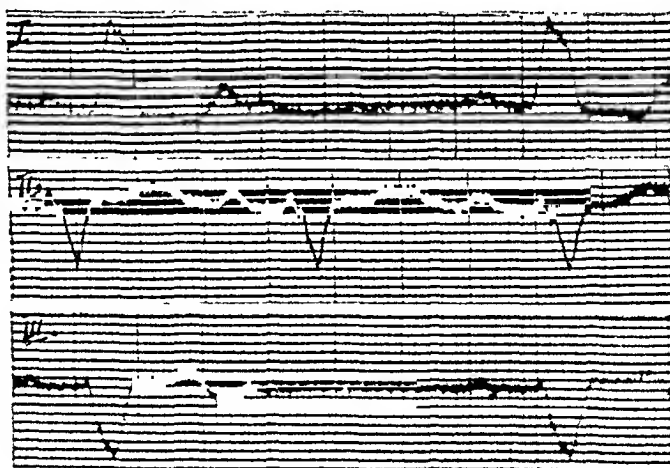


FIG. 6.—Leads I and III show 2-1 block. In lead II the auriculoventricular ratio is 1-1. The PR interval is, however, prolonged.

reported a mortality of 69.6 per cent in a series of 112 cases. The average duration of life in his cases from the time of examination was eight and one-half months. Forty-eight per cent of those studied by Oppenheimer and Rothschild<sup>4</sup> died within two years.

In those instances in which autopsies have been made there has usually been found an advanced sclerosis of the coronary arteries and extensive fibrous myocardial changes. The necropsy findings of 2 cases of this series, of 4 reported by Willius<sup>3</sup> and of 12 studied by Oppenheimer and Rothschild<sup>4</sup> were of this type. In 8 of the fourteen autopsies reported by Oppenheimer and Rothschild<sup>4</sup> there was found an occlusion of the anterior descending branch of the left coronary artery. Four of the cases of our series had severe attacks of anginal pain, suggestive of coronary artery accident, though there is no proof by autopsy of the correctness of such a diagnosis.<sup>5 6</sup>

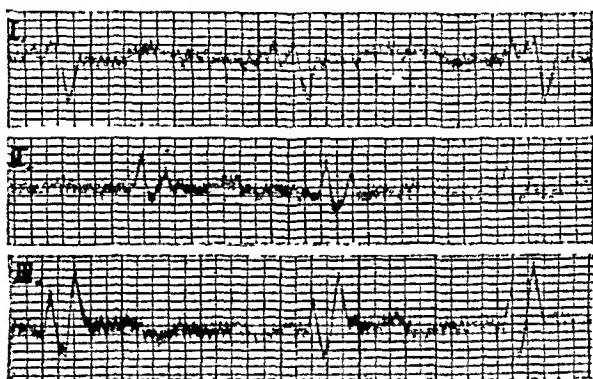


FIG. 7.—Shows very atypical QRS group. The duration is about 0.1 second.

It is to be noted from the histories, clinical findings and autopsy reports of these cases that the changes in the myocardium in a vast majority of the instances are chronic, degenerative in character and are often secondary to arteriosclerosis. The muscular changes are usually extensive. It is for this reason that these types of electrocardiograms are so rarely seen in cases of primary valvular disease. Only one instance of chronic valvular disease has been observed by us that gave an electrocardiogram (Fig. 7) similar to those under consideration. In this patient the myocardial invasion by the primary infection was quite extensive (autopsy).

Any operative procedure of a major character in a patient with this type of electrocardiogram should be considered dangerous even in the absence of advanced clinical cardiac manifestations. It will be noted that 3 of the patients of this group in whom the cardiac conditions were not considered alarming had major operations. Two had very difficult recoveries from cardiac upsets which developed rapidly after the operation. One died suddenly

following the recovery from a prostatectomy, from what seemed to be a cardiac accident. Another died following operation for cataract from thrombosis of the cerebral arteries and of one femoral vein. Another died on the same day after the resection of the left fifth rib for an adhesive pericarditis.

The long duration of the *QRS* group and the direction assumed by the final deflection of these electrocardiograms probably indicate in most instances a block of the impulse over one branch or over a majority of the subdivisions of one branch of the auriculoventricular bundle. These conclusions are in harmony with experimental observations on the dog.<sup>7 8 1 2</sup> In the dog electrocardiograms characteristic of right or left branch block were produced only when these respective branches or a majority of the subdivisions of these branches were divided. The division of the arborization branches alone did not change the electrocardiogram.<sup>7 8 1 2</sup> There were some instances, however, following the cutting of the smaller ramifications to the left ventricle in which the electrocardiogram became atypical after the left ventricle was weakened and dilated as the result of the ligation of branches of the left coronary arteries. In some the electrocardiogram returned to normal after the ligatures were removed from the arteries.<sup>2</sup>

In 32 cases the electrocardiograms conform to the type usually considered as representing defects of the right division. The reasons for making a probable anatomic diagnosis on the basis of this type of electrocardiogram have been considered by one of us in a former report.<sup>2</sup> In this connection, however, it would seem that these points again deserve brief mention. The electrocardiograms under consideration resemble those produced experimentally in the dog by the division of the right branch of the auriculoventricular bundle. This is considered by Lewis<sup>9</sup> as the most convincing reason for making a probable anatomic diagnosis in man on the basis of the electrocardiographic findings. Furthermore, cases have been reported by Eppinger and Stoerk,<sup>10</sup> Cohn and Lewis<sup>11</sup> and Lewis<sup>9</sup> in which the suspected lesion of the right branch was found by histologic examination. Yet Cohn and Lewis<sup>12</sup> found no lesions of the right branch in four instances. In discussing these findings they suggested the possibility of a functional block<sup>13 14 15 16</sup> or in some instances of block of the main stem. Oppenheimer and Pardee<sup>17</sup> have recently recorded two cases in which the lesions were found in the branch other than that anticipated from the electrocardiograms. The findings in one of these cases are not sufficient to offset the above evidence. Further investigation along this line is desirable.

In one instance (Fig. 5, top) the duration of the *QRS* groups varied from 0.06 to 0.15 second. It is assumed that these findings represent a variation in the extent of the interventricular con-

duction defect. The possibility of incomplete bundle branch block was considered.

Three cases produced electrocardiograms in which the chief ventricular deflection was negative in lead I and positive in lead III. This type of electrocardiogram has been held to represent a defect of the left branch. This conception is not supported by experimental studies on the dog but is apparently based solely on a few clinical observations.

**Summary.** 1. Thirty-five cases were studied in which the electrocardiographic findings probably indicate a block of one main branch, or the majority of the subdivisions of one main branch, of the auriculoventricular bundle. The *QRS* groups were atypical in the three leads and exceeded 0.1 second in duration. In many the duration approached 0.15 second. The *T*-wave assumed the direction opposite to that of the prevailing ventricular deflection.

2. In 32 the prevailing ventricular deflection was positive in lead I and negative in lead II and the duration of the *QRS* was prolonged and in many instances approached 0.15 second duration. These electrocardiograms probably represent defects of the right branch.

3. In 3 cases there was an *S*-wave in lead I and *R*-wave in lead III. In these cases the location of the probable lesion of the conduction system is uncertain.

4. In some instances there was a change in the form of the *QRS* group which was coincident with the clinical improvement of the patients. In three there was an increase in the amplitude of the chief ventricular deflections. In one the atypical *QRS* groups disappeared except for a slight increase in duration of the *S*-wave in lead III.

5. All of these patients had symptoms of myocardial weakness. In 17, or 48.5 per cent, there were clinical manifestations of advanced cardiac disease. In nearly all instances the cardiac weakness seemed to be due to a slow degenerative change in the myocardium secondary to arteriosclerosis. Twelve, or 57.1 per cent, of the 21 patients that we were able to follow died within eighteen months. Ten of them died from cardiac failure. Autopsies were done in 3. In 2 there was an extensive sclerosis of the coronary arteries and marked myocardial fibrosis. In the other the anatomic diagnosis was obliterative pericarditis—huge dilatation and hypertrophy of the right auricle and ventricle, moderate hypertrophy of the left ventricle, myocardial fibrosis and cirrhosis of the liver.

#### BIBLIOGRAPHY.

1. Smith, F. M.: Experimental Observations on the Atypical *QRS* Waves of the Electrocardiogram of the Dog, *Arch. Int. Med.*, 1920, 26, 205.
2. Smith, F. M.: Further Observations on Experimental Lesions of the Branches of the Auriculoventricular Bundle of the Dog. In press.

3. Willius, F. A.: Arborization Block, *Arch. Int. Med.*, 1919, 23, 431.
4. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, *Jour. Am. Med. Assn.*, 1917, 69, 429.
5. Herrick J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *Jour. Am. Med. Assn.*, 1912, 59, 2015.
6. Herrick, J. B.: Thrombosis of the Coronary Arteries, *Jour. Am. Med. Assn.*, 1919, 72, 387.
7. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, *Arch. Int. Med.*, 1920, 26, 153.
8. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and the Refractory Period of the Heart of the Dog, *Heart*, 1921, 8, 229.
9. Lewis, T.: The Mechanism and Graphic Registration of the Heart-beat, New York and London, 1920, pp. 117-127.
10. Eppinger and Stoerk: Quoted from Wilson and Herrmann.
11. Cohn, A. E., and Lewis, T.: A Description of a Case of Complete Heart-block, Including the Postmortem Examination, *Heart*, 1912-1913, 4, 15.
12. Cohn, A. E., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart, *Proc. New York Path. Soc.*, 1914, 14, 207.
13. Krumbhaar, E. B.: Adams-Stokes Syndrome with Complete Heart-block without Destruction of the Bundle of His, *Arch. Int. Med.*, 1916, 5, 583.
14. Price, F. W., and Mackenzie, J. W.: Auricular Fibrillation and Heart-block in Diphtheria, *Heart*, 1911-1912, 3, 233.
15. Pepper, W., and Austin, J. H.: Adams-Stokes Syndrome with Complete Heart-block and Practically Normal Bundle of His, *AM. JOUR. MED. SC.*, 1912, 143, 716.
16. Hume, W. E.: A Case of Heart-block in Which There Was No Pathologic Lesion of the Connecting Muscular System, *Heart*, 1913, 5, 149.
17. Oppenheimer, B. S., and Pardee, H. E. B.: Site of the Cardiac Lesion in Two Instances of Intraventricular Heart-block. Read before the American Society of Clinical Investigation, Atlantic City, May 3, 1920.

## POST-TRAUMATIC CALCIFICATION OF THE PANCREAS, WITH DIABETES.

BY H. GIDEON WELLS, M.D.,

CHICAGO.

(From the Department of Pathology, University of Chicago, and the Otho S. A. Sprague, Memorial Institute.)

THE condition described in the above caption is, as far as some search through the literature seems to indicate, altogether unique, and hence a case illustrating it is herewith reported in some detail, especially since evidence bearing on the relation of the pancreas to diabetes is also of value.

The subject was a man, aged thirty-two years, a teamster, who while driving his wagon fell from the seat. As to whether the wheels of the wagon passed over his body or not the evidence of bystanders was conflicting, but from the nature of the injuries found at the autopsy there can be no doubt that they did. This happened on March 31, 1919, and he was at once taken to the Cook County Hospital. The examination on his admission showed him

to be under the influence of alcohol, with the left sixth, seventh, eighth and ninth ribs fractured in the axillary line and considerable subcutaneous emphysema. No other injuries could be found, and, as far as the records show, no urinalysis was made. There was elicited a history of a fracture of an arm two years previously and of habitual alcoholism, but no evidence of any illnesses. He remained in the hospital until April 12, when he was discharged as recovered from the fractured ribs.

August 17, he was brought back to the hospital in an irrational, slightly stuporous condition, much emaciated and evidently seriously ill. It was learned that shortly after his return home a suppuration appeared on the inner side of the right elbow, which had not been observed to be injured while in the hospital, and from this there had been continuously a slight discharge of pus. His relatives stated that he had not been normal mentally since the accident, and he had been unable to work; he was irritable, stupid and made mistakes in conversation and in action. There was a progressive and marked loss of weight, estimated at about twenty pounds, although he had been slender previously. For three weeks previous to his return to the hospital he had been having typical attacks of Jacksonian epilepsy, increasing progressively in frequency and severity. The onset of each attack was with a sensation of stiffening in the left foot, followed by twitching and jerking which spread up the left thigh to involve the abdominal and chest muscles, then extended to the right lower extremity, then both upper extremities, beyond which the patient has no recollection. Sometimes the attacks were at intervals of not over one-half hour.

Observed in an attack in the hospital the patient began by having clonic spasms of the left lower extremity, then he stiffened his trunk and his arms began to jerk, his hands half closed, the fingers extended and shook; his mouth was half-open, his lower jaw moving in jerks, his facial muscles twitched and his eyes rolled. At the beginning of one of these spasms the patient gave successive loud cries. The spasms continued for about one or two minutes, and then the patient relaxed in about fifteen to thirty seconds; he was almost immediately conscious after the jerking stopped. There was no previous history of scalp injury, except being hit with a beer bottle about five or six years before; the blow dazed him for ten to fifteen minutes.

The only other information obtained was that he had had a slight cough for about a year and that he had had gonorrhea but not syphilis. On entering the hospital he complained of weakness, loss of appetite, nausea and great thirst. His relatives stated that for some time after his accident he had been noted to be extremely thirsty, drinking large quantities of water. Also he had complained of itching.

Urine had been passed during the convulsions, and so no estimate of polyuria was obtainable.

The chief physical findings on readmission to the hospital were the following:

The patient is a white man of about thirty-two years of age, of medium height, emaciated and in a slightly stuporous condition. There is a thickening of the end of the humerus at the internal condyle, with a slight stiffness of the elbow. A sinus opens about 4 cm. above the lower portion of the internal condyle, discharging a small amount of seropurulent fluid.

*Teeth.* Carious.

*Tonsils.* Moderately enlarged; rest of head negative.

*Neck.* Negative.

*Chest.* Symmetric and emaciated; clavicles prominent. The semistuporous condition of the patient makes it difficult to obtain findings. Rales present over the whole chest, specially the lower lobes.

*Heart.* Apex not palpable. Left border  $\frac{1}{2}$  cm. from midline, right border substernal. Rate, 128. First sound weak, second pulmonic accentuated. No murmurs.

*Abdomen.* Retracted and tense. Liver dullness, sixth interspace to costal margin. Kidney and spleen not palpable. No masses or tender spots.

*Genitalia.* Negative.

*Extremities.* Negative except for right elbow as mentioned. Reflexes exaggerated on left side. Some spasticity on left side.

*Clinical Diagnosis.* Chronic osteomyelitis of the right lower third of the humerus. Jacksonian epilepsy of undetermined etiology.

During the forty-eight hours that the patient was in the hospital he had repeated convulsions, during which urine was passed, and as there were no special indications of urinary change, no effort was made to secure specimens, so we have no record of the composition of the urine. The Jacksonian epilepsy dominated the picture completely, and he died in *status epilepticus* on August 20, and an autopsy was performed eight hours after death.

The autopsy findings were as follows:

*External Appearance.* The body is that of a small, poorly built, poorly nourished white man. *Rigor mortis* in legs and fingers. No edema. No icterus. No adhesions between the scalp and the skull. No evidence of trauma to head. Superficial lymph glands not enlarged. External genitals normal. No subcutaneous fat. On the inner aspect of the right elbow there is an elliptical opening in the skin, 10 by 20 mm., with a granulating floor, and the skin is much undermined. When cut through there is a superficial suppurating area between the skin and the muscle fascia anterior to the internal condyle, extending down into the internal condyle, where there is a suppurating cavity 1 cm. in diameter.



*Abdominal Cavity.* The inguinal and femoral rings are closed. Omentum is free from fat and adherent about the cecum. There are small hard lymph glands in these adhesions. The appendix lies behind the cecum and is remarkably kinked on itself, forming a T, and is bound down by adhesions. There are also numerous vascular tags of adhesions over the sigmoid and elsewhere on the intestines. The mesenteric lymph glands are all slightly enlarged, pale and hard. The surface of the bladder is covered by a vascular connective tissue. There are numerous folds and bands of adhesions throughout the pelvis. The omentum is black from pseudomelanosis. There are dense fibrous adhesions about the spleen. There are also a few adhesions about the gall-bladder, elsewhere the liver is free. The peripancreatic glands are slightly enlarged. The retroperitoneal glands are normal in size.

*Pleural Cavity.* The left pleural cavity is partly obliterated, laterally and over the base, by dense fibrous adhesions. The right pleural cavity is completely obliterated. When the sternum was removed small pockets of pus were seen between the diaphragm and the lower margin of the right lung and chest wall. There is a hard white lymph gland present in the anterior mediastinum 1 cm. in diameter. Healed fractures of the sixth and seventh ribs can be felt on the left side at the anterior axillary line, with some overriding of the ends. Here the pleural adhesions are most dense. The lymph glands about the hilum of the left lung show small suppurating areas. There are numerous (twenty to thirty) small pockets of thick greenish-yellow pus lying beneath the parietal pleura on the right side, irregularly placed all over the cavity, in size up to 2 cm. in diameter. There are also a few such cavities within the pleural adhesions, specially between the diaphragm and the chest wall. No abscesses are found outside of the chest cavity or on the left side. There are no old fractures or other evidence of trauma on the right side. No subdiaphragmatic lesions.

*Pericardial Cavity.* Contains normal amount of fluid. There are protruding hyperemic areas showing through the left lateral aspect of the pericardium over the subpleural abscesses. The lining is smooth and not involved by this process.

*Heart.* Slightly enlarged. The left ventricle takes up the greatest area. There are small beaded areas in the coronary arteries. The right and left posterior cusps of the aortic valves are fused to each other by a soft fibrinous adhesion. The beginning of the aorta is nearly free from sclerosis. There is very little sclerosis in the thoracic aorta. Ductus arteriosus is closed. The tricuspid and mitral orifices are of normal size. The tricuspid and pulmonic valve cusps are normal. Along the free margin of the mitral valve, throughout its circumference, is a fresh growth of recent soft vegetations 1 to 3 mm. thick. Foramen ovale is closed. The walls of the ventricles are of normal thickness. The left

ventricle is stopped in diastole. The myocardium is slightly mottled in appearance; there are no definite macroscopic changes. The empty heart weighs 300 gm.,

*Trachea.* Normal.

*Peribronchial Lymph Glands.* No caseation or calcification; some contain small suppurating foci.

*Esophagus.* Normal.

*Lungs.* The left lung is inelastic and there are no definite areas of consolidation; weight, 600 gm. The lower lobe is very dark in color and contains much fluid. Every bronchus when cut is filled with creamy pus. The upper lobe shows the same condition, particularly in the posterior portion, less marked anteriorly. The right lung is covered with adhesions. Weight, 840 gm. There are some hard scars in the apex, especially the posterior part. Abscesses as described above are noticed in the pleural adhesions. There are also some small areas of hemorrhage in the pleura. Section through the upper lobe shows a distinct cavity 18 to 20 mm., running from which are lines of scar tissue. There is a caseous nodule at the upper apex 10 by 12 mm. Another small cavity is found in this upper lobe. There are some small gray tubercles in the peribronchial lymph gland that receives the drainage from the right upper lobe. There are no other definite areas of consolidation.

*Spleen.* Embedded in adhesions. Weight, 70 gm. The upper pole alone remains. The lower pole is hard, yellow, shrunk and covered with adhesions. When cut the entire lower pole is found to be replaced by a well-defined encapsulated necrotic mass, 5 x 4 x 3 cm. The rest of the spleen is very soft and pulpy.

*Kidneys.* The left kidney is surrounded by a mass of flabby fibrofatty tissue which is very adherent to the kidney. There is a total infarction of the left kidney. The size of the left kidney is approximately  $5\frac{1}{2}$  x 4 x  $1\frac{1}{2}$  cm. The structures are left in recognizable form but yellow and completely necrotic, without suppuration. The left renal artery is much smaller than the right and completely obliterated at the hilum of the kidney. Right kidney large, weight, 200 gm., soft. Cut surface shows cortical markings distinct. Cortex thick, 8 to 10 mm. There are no signs of abscesses. The capsule strips readily leaving a smooth surface.

*Adrenals.* Right adrenal seems normal in size and appearance. Left adrenal is normal except for one island of white tissue (5 x 10 mm.) in the medulla.

*Liver.* Dark in color and soft. Weight, 1900 gm. The cut surface shows considerable blood. The center of the lobules are dark. The cut surface is very wet. No other changes. Gall-bladder: Normal. No concretions.

*Pancreas.* More rounded and thin than normal. Weight, 122 gm. The irregularity increases from head to tail. Head is distended with a mass the size of a hen's egg. Upon palpation the entire pancreas is full of small hard lumps, feeling as if filled with small stones. These concretions can be felt throughout the pancreas, about equally in all parts. They are all embedded in the tissue and a watery purulent fluid exudes from the ducts. They are not loose in the duct but are in the tissue itself, mostly firmly adherent; a few protrude into the duct, apparently by erosion from the outside. There are areas of partial stenosis along the pancreatic duct, but it is not anywhere completely obstructed. A few small concretions are found free in the duct. The entire pancreas is composed of scar tissue and calcified masses, no normal gland tissue being found. There is an increase in the peripancreatic fibrous tissues, but no concretions are found outside the gland tissue.

*Stomach.* Postmortem digestion. No lesion. Intestines: Normal.

*Urinary Bladder.* Greatly thickened with some hypertrophy of trabeculae. Mucosa normal. *A small quantity of wine was present which contained 2½ per cent of sugar.*

*Prostate.* Somewhat enlarged and forms a ring about the urethra. There are no other gross changes. Seminal vesicles normal.

*Testicles.* Both normal.

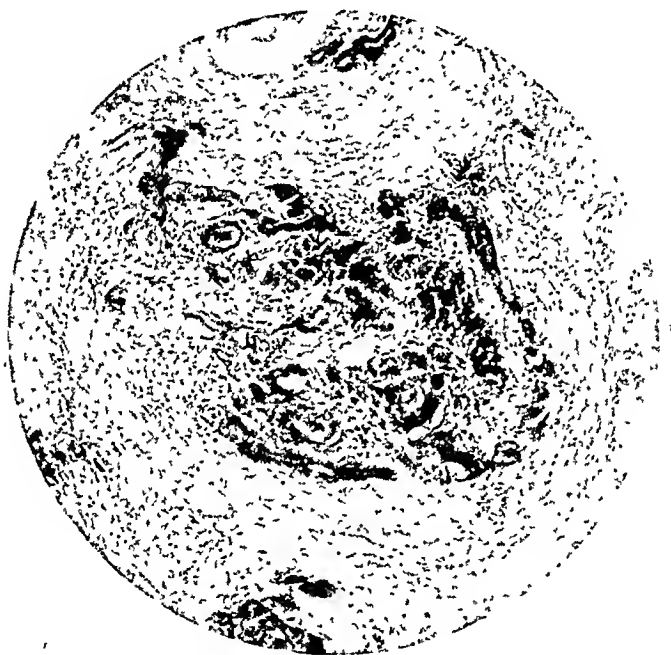
*Skull.* The calvarium is normal. The dura on the external surface appears normal. There is no undue tenseness. There is a considerable amount of cerebrospinal fluid both between the dura and pia arachnoid and in the pia arachnoid. This fluid is clear.

*Brain.* Weight, 1500 gm. There is a diffuse reddish discoloration of the pia over the right lateral aspect, particularly at the junction of the frontal and parietal lobes. Elsewhere the pia is clear. There is an area of softening 4½ cm. long by 2 x 2½ cm. wide, involving the ascending frontal and ascending parietal convolutions in this area, the upper margin of the softening being 3 cm. from the midline. There is no evidence of suppuration in the meninges. The softened area averages 5 to 10 mm. thick, involving the gray matter chiefly. The lateral ventricles are of normal size, containing a clear fluid. The basal ganglia appear normal.

*Anatomical Diagnosis.* Infarction with softening of the right ascending frontal and parietal convolutions. Multiple subpleural tuberculous abscesses in the right chest wall. Bilateral hypostatic congestion and acute suppurative bronchitis. Bilateral adhesive fibrous pleuritis. Acute terminal mitral and aortic endocarditis. Complete anemic necrosis of the left kidney with compensatory hypertrophy of the right kidney. Healed anemic necrosis of lower three-quarters of the spleen. Extensive fibrosis and calcification of the entire pancreas. Pancreatic diabetes (glycosuria).

Healed fractures of the sixth and seventh left ribs. Abscess in internal condyle of right humerus with fistulous cutaneous opening. Parenchymatous degeneration of the liver and the right kidney. Hypertrophy of the urinary bladder wall. Healed appendicitis. Ulcerative and fibroplastic tuberculosis of the right pulmonary apex. Suppurative tuberculous mediastinal lymphadenitis. Hyperplastic tuberculosis of the mesenteric lymph glands. Healed necrotic area in the left adrenal. Healed diffuse peritonitis.

**Histological Examination.** *Pancreas.* The pancreas shows an extreme grade of fibrotic pancreatitis. (See Figure.) A small



Traumatic pancreatitis. This was one of the few islands of pancreatic tissue still present, located near the duct in the head of the pancreas. As will be observed, it consists chiefly of duct-like tubules rather than secretory structures, and these are isolated and compressed by scar tissue. Magnified 45 diam.

number of isolated, shrunken pancreatic islets remain, many being partially fibrosed. Besides these there are only traces of pancreatic tissue, although occasionally necrotic remains of pancreatic gland cells are found, barely recognizable. There are innumerable areas of calcification throughout the organ, each surrounded by dense fibrous tissue. The amount of replacement by fibrous tissue is so great that it is impossible to determine whether the calcific deposits are exclusively intra-alveolar or not, but certainly most of the calcium is deposited in the sites of necrotic glandular masses. Besides the large calcified masses the tissue is sprinkled everywhere with minute quantities of calcium salts, replacing small

groups of dead epithelial cells. No calcification of the vessels or of the fibrous septa is observed. Occasional islands of fatty areolar tissue remain within the fibrous masses, but these are never found calcified. No blood pigment is found.

Among the few small foci of recognizable glandular tissue that remain are many that consist of cells that have lost their nuclear staining and are surrounded by very heavy masses of fibrous tissue. A little pancreatic tissue that seemed capable of functioning is seen in only a few of the several parts of the gland that were examined, chiefly about the ducts near the head of the pancreas. These consist of the remains of lobules, with a dense fibrous capsule about them, fibrous tissue infiltrating between the atrophic tubules and ducts that remain, and occasionally a small atrophic Langerhans islet is recognizable. Nowhere is any area of even approximately normal pancreatic tissue to be found. It would seem that over 95 per cent, and probably fully 99 per cent, of the secreting pancreatic tissue has been replaced by fibrous tissue and calcium salts. There are no evidences of inflammation present, either tuberculous or acute.

*Heart.* The valves show recent vegetations. The myocardium is normal.

*Lungs.* The lungs show both old encapsulated and active tuberculosis, as well as acute hypostatic pneumonia and acute bronchitis.

*Lymph Glands.* The glands, particularly the intrathoracic glands, exhibit caseous and encapsulated tuberculosis, often with softening. The mesenteric and retroperitoneal glands show small tubercles, with much endothelial hyperplasia.

*Adrenals.* The left adrenal gland exhibits an extensive fibrotic area at the center, containing considerable blood pigment, apparently representing the site of a healed traumatic lesion. Elsewhere the adrenals are normal.

*Liver.* Shows no changes.

*Kidneys.* The right kidney shows a distinct increase in the size of the glomerules and tubules, without other noteworthy changes. The left kidney is completely necrotic, without sign of infection. Much thickening of the pericapsular tissues. The original structures are all visible but totally unstained.

*Brain.* Shows an old infarct with abundant blood pigment in phagocytes. The absorption of the necrosed tissue seems to be complete.

*Spleen.* The necrotic portion resembles a typical old infarct, with abundance of blood pigment, both granular and crystalline. The remaining living portion shows large Malpighian bodies and some blood pigment in the pulp.

*Chemical Analysis of the Pancreatic Tissue.* Samples from several parts of the alcohol-fixed gland were selected, to give a fair average

of the composition, and the inorganic material determined. In 0.9546 gm. of dried material was 0.6100 mg. of inorganic residue, or 63.9 per cent.

Several of the calcified masses were picked out of the pancreas and separated as completely as possible from tissue elements. They were analyzed for me by Miss Mary E. Maver, using the wet method used in my previous work on calcification, which method avoids the errors introduced by ashing.<sup>1</sup> Two such lots were analyzed at different times, and the following results were obtained:

## PANCREATIC CALCIFICATION.

	Sample I.		Sample II.		Average per cent.
	Gm.	Percentage of inorganic.	Gm.	Percentage of inorganic.	
Ca . . . . .	0.3765	35.6	0.1110	38.9	37.25
Mg . . . . .	0.0028	0.27	0.0028	0.9	0.63
CO <sub>2</sub> . . . . .	0.2725	25.9	0.0696	24.2	25.05
P . . . . .	0.0141	1.33	0.0008	0.27	0.80

Theoretically the inorganic elements existed as follows:

CaCO <sub>3</sub> . . . . .	0.8848	92.7	0.2738	95.20	93.95
Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> . . . . .	0.0585	6.1	0.0040	1.39	3.74
MgCO <sub>3</sub> . . . . .	.....	.....	0.0098	3.4	
Mg <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> . . . . .	0.0103	1.08			

From these figures it is seen that the concretions consisted chiefly of calcium carbonate with but small quantities of calcium phosphate and magnesium salts. About 20 per cent of the calcium found could not be balanced with acid radicals. Search was made for oxalic acid and fatty acids, with which the calcium might have been united, but neither was obtained. It is observed that the analysis of two different lots agreed quite closely as far as the CO<sub>2</sub> was concerned, so it was certain that there was no loss in this determination. Thorough extraction with boiling amyl alcohol failed to dissolve out any calcium soaps. No silicate was present, a point of some interest, since some German writers have laid stress on the function of the pancreas as a storehouse for silicates and as a center of silicic acid metabolism.

This high proportion of calcium carbonate is entirely different from the figures usually obtained in analysis of calcified tissues, in which generally about 85 per cent of the inorganic material is calcium phosphate and about 10 per cent is calcium carbonate.

<sup>1</sup> Wells: Jour. Med. Res., 1906, 14, 491.

On the other hand our figures agree closely with some of the figures given for caleuli found in the pancreatic ducts. Thus, Möckel,<sup>5</sup> in his compilation on pancreatic caleuli, gives the following figures reported in the literature: I,  $\text{CaCO}_3$ , 91.65 per cent (Johnston, Moynihan). II,  $\text{CaCO}_3$ , 82.0;  $\text{Ca}_3(\text{PO}_4)_2$ , 12.7 per cent (Maurice, Lussac). III,  $\text{CaCO}_3$ , 93.14 per cent;  $\text{P}_2\text{O}_5$ , 2.45 per cent (Legrand, Scheunert). Other analyses of pancreatic caleuli, however, have shown the chief constituent to be calcium phosphate. Presumably the predominance of calcium carbonate in pancreatic caleuli, as well as in this one specimen of calcification of the pancreatic tissue, depends on the fact that the pancreas secretes a fluid alkaline with carbonates, since we find that the salivary duct caleuli also sometimes consist chiefly of calcium carbonate, although these also may at times contain chiefly calcium phosphate.<sup>2</sup>

**Discussion.** The history and the autopsy findings establish this as a case of post-traumatic calcification of the pancreas with diabetes. The fractured left ribs, the traumatic infarction of the left adrenal, the left kidney and the upper pole of the spleen indicate that the changes of the pancreas were also the result of traumatism to the left side and the upper abdomen. Probably the wheel of the wagon went across the lower chest and the upper abdomen, since merely a fall from this height could scarcely have produced this amount of injury in these deep-seated organs. The history of great thirst, pruritus and progressive emaciation after the accident, together with the presence of sugar in the urine and the very extensive destruction of the pancreas, establish the diagnosis of traumatic pancreatic diabetes. The acute tuberculous changes in the pleura and lymph glands may be the result of the diabetes, although it is impossible to determine that they may not have been incited by the trauma in a subject with an existing pulmonary tuberculosis. Also, it is not certain whether the area of cerebral softening that caused the Jacksonian epilepsy was the result of the fall or had come from embolism; the histology of the brain lesion, however, suggests that it was contemporaneous with the lesions in the spleen, kidney and adrenal, and the history stated that the patient had never been normal mentally after the accident. The endocarditis was distinctly a terminal infection and too recent to have caused the lesions in the kidney, spleen, adrenal and brain.

The calcification seems to be distinctly of the pancreatic glandular tissue itself and is not the result of pancreatic fat necrosis, for not only were there no calcified foci in the fat tissue outside the pancreas, but even the fat tissue within the pancreas itself showed no calcification.

It is unfortunate that the patient was not brought into the

hospital until he was in a dying condition, and hence we have no data on the urine and the changes in the intestinal digestion that had resulted from so extensive a destruction of the pancreas.

**Discussion of the Literature.** As stated, no similar case can be found recorded. The extensive discussion of pancreatic cysts and concretions by P. Lazarus<sup>3</sup> makes no mention of calcification of the pancreatic tissue from any cause whatever nor of the occurrence of pancreatic calculi following trauma. He describes several cases in which scars and cysts have followed traumatism, but does not speak of calcification in connection with these. He also states that up to that time (1904) no case of diabetes had been described as a sequel of a traumatic cyst of the pancreas. Of interest in connection with our case is his statement that the most common cause of pancreatic trauma is being run over by vehicles and that the injuries are seldom of the pancreas alone, the liver, kidneys and spleen being often traumatized, as well as the ribs and the vertebral column. He also calls attention to the fact that only a part of the traumatisms of the pancreas are followed by fat necrosis, indicating that some added factor, such as infection or inflammation, must be present to produce this complication.

Opic in his monograph on *Diseases of the Pancreas* makes no mention of calcification of pancreatic tissues, nor does Kauffmann in his *Text-book of Pathologic Anatomy*. Numerous articles on pancreatic concretions have been reviewed, but in none of them do we find mention of calcification of the pancreas itself, except the statement in the article by Weichselbaum and Stangl<sup>4</sup> on the pancreas in diabetes that "in one case we demonstrated calcium deposits in the hyaline or sclerotic islands, whereby an increased similarity is given to sclerotic renal glomeruli." Neither is trauma mentioned as a cause of pancreatic calculus formation.<sup>5</sup>

While a complete search of all the literature on diabetes for cases of diabetes following trauma to the pancreas has not been possible because of the magnitude of the task a large number of articles and monographs have been reviewed, including practically all of the larger publications, virtually without finding any mention whatever of pancreatic trauma as a possible cause of diabetes. This is not strange in view of the fact that the pancreas is so well protected that only the most violent traumatism can injure it, and then the results are usually quickly fatal; if not fatal there is probably usually sufficient pancreatic tissue left to prevent diabetes. For example, Robeson and Cammidge in their work on the pancreas state that Garré was able to collect but 30 cases of pancreatic trauma, of which 3 recovered. Naunyn does not mention the possibility of diabetes as a result of trauma to the pancreas,

<sup>3</sup> Zeit. klin. Med., 1904, 51 and 52.

<sup>4</sup> Wien. klin. Wchnschr., 1902, 15, 972.

<sup>5</sup> Literature given by Mückel, Frankfurter Zeit. f. Pathol., 1920, 24, 78.



but comment on the infrequency of diabetes following acute pancreatitis. Even the work devoted specifically to surgical diseases and injuries of the pancreas by Korte<sup>8</sup> makes no mention of calcification of the pancreas or post-traumatic diabetes. So, too, the works of von Noorden and Lépine are silent on this subject; the latter does mention traumatic diabetes as if depending entirely on nervous lesions, yet of 115 cases of traumatic diabetes collected by him in 8 the trauma is said to have been abdominal. Arnstein<sup>9</sup> in an elaborate review of 437 articles on chronic pancreatitis does not even mention either traumatic pancreatitis or calcification of the pancreas.

Jeancloue<sup>5</sup> reported, in 1897, 2 cases of bronzed diabetes, one of which, in a man aged forty-three years, was observed first a short time after receiving a blow near the umbilicus. The exact interval between the injury and the appearance of the symptoms of diabetes (marked thirst, anorexia, polyuria and loss of strength) is not given. It could not have been more than a few days, however, since it is said that the blow was received "at the beginning of the month of July," and the symptoms were said to have appeared about the 16th to 18th of the same month. Furthermore, nothing is said about the condition of the patient in the intervening time. Autopsy was performed on the fourth of the following January and disclosed the classic features of bronzed diabetes. The pancreas weighed 150 gm. and was irregularly pigmented. Microscopically it was sclerotic, although some lobules were little altered. Nothing was said in the autopsy report about the presence of any evidences of trauma in the abdominal cavity or elsewhere. With these scanty data it is not possible to prove that in this case the diabetes was the result of the abdominal traumatism, and it is highly doubtful that a traumatism to the pancreas could cause a bronzed diabetes in view of the evidence that in this disease the pancreatic sclerosis is the result of deposition of pigment in the pancreas.

In his work on the traumatic origin of internal diseases, Richard Stern<sup>9</sup> comments on the fact that in no published case of injury to the pancreas has glycosuria been observed.

We have found but one probably authentic case of post-traumatic pancreatic diabetes reported in the literature, by Gruncl.<sup>10</sup> The patient, a woman, aged twenty-five years, while six months pregnant, slipped on the ice and another person fell across her abdomen. After a period of abdominal pains and vomiting all symptoms subsided and a healthy child was delivered at term. A

<sup>8</sup> Die Chirurgischen Krankheiten und die Verletzungen der Pankreas, Stuttgart, W. Korte, 1898.

<sup>7</sup> Centr. f. d. Grenzgeb. d. Med. u. Chir., 1912, 15, 90.

<sup>8</sup> Bull. et mém. de la Soc. méd. des Hôp. de Paris, 1897, 3d series, 14, 179.

<sup>9</sup> Ueber traumatische Entstehung inner. Krankheiten, Jena, 1913, 2d ed.

<sup>10</sup> Mitt. u. d. Grenzgeb. d. Med. u. Chir., 1907, 17, 395.

month later pain and vomiting recurred with icterus, there being intervals of good health, with the gradual development of mild diabetes. About a year after the trauma a pancreatic cyst was operated on. The icterus subsided at once and permanently, but the diabetes persisted and within a few months assumed a comparatively severe form. The metabolic findings are tabulated as recorded during the various phases of the case; they show that the functions of the pancreas in respect to the digestive processes were not essentially altered. At the time of the publication of this report the patient was still living, and so we lack anatomic proof of the pathologic changes present.

The only instance of calcification of the pancreas tissue itself of which we can find record, beyond the apparently trivial involvement mentioned by Weichselbaum and Stangl, has been reported by Bernhard Fischer,<sup>11</sup> who states that it is, as far as he knows, a condition never previously described. The subject was a youth, aged eighteen years, with a striking family history of diabetic relatives, who had typical juvenile diabetes terminating in coma. There was no history of any trauma mentioned. The autopsy disclosed nothing of significance outside the pancreas, which was of normal size (100 gm.) and color, somewhat indurated, and showing macroscopically on the cut surface numerous tiny white calcific points, compared to the calcified glomerules in senile kidneys. Microscopically the changes were remarkable, for not only were the number and size of the islands of Langerhans enormously increased, but most of them showed calcification, often extensive, as well as sclerosis and hyaline degeneration. Some of the islands were so enlarged as to resemble adenomas, one of them being 1.3 mm. in diameter, and the number was so great that there must certainly have been a new formation of islands. The calcium salts stained with silver nitrate, and hence were presumably phosphatic, at least in part. Fine droplets of fat were sometimes found in the calcified islands. The connective tissue was considerably increased throughout the pancreas, but the glandular parenchyma was little altered. There was some calcification in the internal elastic lamina and the inner layers of the media of the arteries, but none in the parenchyma or stroma of the pancreas outside the islands. There was nothing found to explain why this remarkable selective calcification of the islands had occurred. Presumably they had undergone hyaline degeneration and then this hyaline material had become calcified as hyaline deposits everywhere are prone to do, perhaps because of a physical affinity for calcium salts.

Of course in pancreatic fat necrosis the freed fatty acids unite with calcium to form soaps, which might perhaps become converted

<sup>11</sup> Frankfurter Ztschr. f. Path., 1915, 17, 218.

into phosphate and carbonate, although my own experiments indicate that the lesions of fat necrosis may disappear entirely within a short time,<sup>12</sup> and that implanted soaps are mostly reabsorbed rather than replaced by the less soluble phosphate and carbonate.<sup>13</sup>

**Summary.** . A previously healthy young man fell from a wagon and was probably run over by at least one of the wheels. He received fractures of several ribs on the left side, traumatic infarction of the left adrenal, the upper pole of the spleen and the entire left kidney, together with a crushing injury of the pancreas, which resulted in almost complete destruction of the secreting elements, which were replaced by a large quantity of dense fibrous tissue and extensive deposits of calcium salts. Analysis showed that about 64 per cent of the dry weight of the pancreas consisted of inorganic salts, chiefly calcium carbonate. Jacksonian epilepsy developed, the result of necrosis of a considerable area of the cerebral cortex, presumably occurring at the same time as the other injuries. The patient became rapidly emaciated, exhibited great thirst and the urine found in the bladder at autopsy contained sugar. A review of the literature has failed to reveal a similar case of extensive pancreatic calcification, whether post-traumatic or otherwise, or an analogous case of diabetes following crushing injury of the pancreas.

## QUANTITATIVE STUDIES IN SYPHILIS FROM A CLINICAL AND BIOLOGIC POINT OF VIEW\*

By JOHN A. FORDYCE, M.D., ISADORE ROSEN, M.D.;

AND

C. N. MYERS, PH.D.,

NEW YORK.

(From the Department of Dermatology and Syphilology, and the Department of Biologic Chemistry, College of Physicians and Surgeons, Columbia University, New York.)

### PART I. ANALYTICAL METHODS.

CLINICAL medicine has for a long time felt the necessity of correlating its work with the biologic laboratory where definite chemical reactions and tests are employed to reveal the end-results of body function. During the past decade biologic chemistry has advanced with enormous strides and has yielded invaluable aid to the clinician, as the study of blood chemistry alone will show. Syphilis therapy, too, owes in a large measure its success to this branch of medicine,

<sup>12</sup> Jour. Med. Research, 1903, 9, 70.

<sup>13</sup> Ibid., 1907, 17, 15.

\* Received for publication, February 2, 1922.

for the progress made in the treatment of this disease with the newer arsenicals would have been impossible without the experimental research carried on in animals.

Since the introduction of arsphenamin into the realm of therapeutics many questions have been in debate, especially those concerning the amount of arsenic in the body fluids, or, more specifically, the blood and spinal fluid. Through the courtesy of Prof. Gies, of the department of biologic chemistry, College of Physicians and Surgeons, who has been kind enough to aid us in our undertaking, we have carried on a series of studies during the past two years. Originally it was our intention to examine about 100 specimens to determine (a) the amount of arsenic found in the blood at different intervals after intravenous injections of arsphenamin, and (b) whether arsenic is present in the spinal fluid after intravenous medication. As the work progressed new problems presented themselves which required the study of other phases of this subject and led to our analyzing about 2000 specimens.

Owing to the lack of hospital facilities we were able to investigate only the urine, blood and spinal fluid. These being the most important fluids of the body, we hope the data obtained will be of value in deciding a number of debatable questions.

In our work we have taken into consideration the fact that there is probably a decided variation in the amounts of arsenic found in these fluids, the dosage being the same, in individuals of different age, weight, sex and state of health. This will be discussed in detail in a paper which will appear later. The important question whether arsenic finds its way into the spinal fluid will be considered not only from a theoretic standpoint but from the results of numerous examinations of spinal fluids from patients treated intravenously.

Our studies, which will appear in several instalments, include the following problems:

1. When is the largest amount of arsenic found in the blood after an intravenous injection?
2. Is there a difference in the arsenic content of the blood serum and the elot?
3. When is the largest amount of arsenic found in the urine?
4. What is the variation in the amount of arsenic found in the blood and the urine at the same intervals?
5. Does the use of normal saline in the preparation of the solution exert any influence on the amount of arsenic demonstrable in the blood and urine?
6. Is the arsenic content in the blood and urine related to the stage of the disease? Is there any differences in these fluids from early, late, latent and Wassermann-fast cases as well as non-syphilitic patients?
7. What is the quantity of arsenic present in the blood and

urine at varying intervals after intramuscular injections of neoarsphenamin?

8. Does the amount of arsenic in the blood and urine vary according to the preparation employed, namely, arsphenamin, neoarsphenamin and silver arsphenamin?

9. Can arsenic be demonstrated in the blood and urine months after the cessation of treatment?

10. (a) Do patients who develop arsphenamin jaundice show an excess of arsenic in the blood and urine?

(b) Can arsenic be demonstrated in these patients at longer intervals after the cessation of treatment than in non-jaundiced cases?

11. (a) Is arsenic demonstrable in the spinal fluid after intravenous injection?

(b) Can it be found in all cases or in only a certain percentage?

12. When after an intravenous injection is the largest amount of arsenic found in the spinal fluid?

13. Is the quantity increased when intensive intravenous treatment is employed, *i. e.*, daily injections for three doses?

14. Does the amount of arsenic present in the spinal fluid vary with the preparation used, *i. e.*, arsphenamin, neoarsphenamin or silver arsphenamin?

15. Does the type of neurosyphilis play a role in the quantity of arsenic present in the spinal fluid?

16. Does intraspinal treatment influence the amount of arsenic found in the spinal fluid at future examinations?

17. Is there any relationship between the strength of the Wassermann reaction of the spinal fluid and the amount of arsenic present?

18. Does a relationship exist between the type of colloidal gold reaction and the amount of arsenic found?

19. Is there a relationship between the amount of globulin found in the spinal fluid and the quantity of arsenic present?

20. In what quantities is arsenic present in the milk of treated nursing syphilitic mothers?

The fact that arsenic, by whatever channel absorbed, causes tissue changes (and the symptoms resulting therefrom fairly warrant the inference that it enters into chemical reaction with the constituents of those tissues) and if it disappears therefrom sooner than it does from the liver and other parenchymatous organs—it is because the form of combination is less stable in the one case as compared with the former. Upon this basis the use of arsenic is to be upon distinct physical, chemical and dynamic fundamental as applied to the therapeutic treatment of disease. Based upon the above conception, it immediately became evident that arsenic, and an inactive variety of arsenic should exist in that the amount that is eliminated is rapidly had little or no opportunity to react or any irritating effects and that the amount left is so small that it may be a cause for many Wassermann reactions.

As early as 1839 arsenic was detected in the blood drawn from the veins of the human subject in life, whereas Seidel (1882) reported that arsenic is found in the corpuscles but not in the plasma. In the light of our present knowledge slightly different views are held.

In a succeeding paper absorption, elimination, retention and the normal values will be discussed for the reason that each of these subjects needs considerable elaboration. It is quite necessary to make a few of these preliminary remarks that it may be clear that the subject arsenic is not new, that the methods of elimination are being rediscovered, that the analytic procedures are not unusual or novel.

The opening paragraphs very aptly point out the problems which may be elucidated by the application of a large variety of procedures which have not been utilized with uniformity together with accurate clinical study.

Elimination of arsenic begins very early and takes place during the progress of its absorption. Elimination takes place through the urine, the feces, the epidermic tissues and to some extent by perspiration, the breath, milk and menstrual blood (Segale, 1904).

With these possibilities of elimination it is immediately apparent that only the more accessible modes of elimination can be studied, and, furthermore, the amount *retained* is the part of essential interest.

The systematic removal of arsenic from other extraneous material, both organic and inorganic, has been the subject of much study for more than a century. These systematic contributions have offered many modifications, and it may now be said that quantitatively accurate methods are available for determining minute quantities of the element.

Generally speaking the analyst thinks of three methods for determining arsenic toxicologically or for use in medical jurisprudence where delicacy and accuracy are involved. These methods are generally spoken of as the Reinsch, Marsh and Gutzeit tests. These three methods will be briefly spoken of later. In addition the method of Schneider and Fyfe (sometimes spoken of as the method of Liebig-Ludwig), based upon the separation of the arsenic as the trichloride in the presence of ferrous chloride, has been utilized. It is a distillation method, and it is hardly reliable in estimating minute quantities of arsenic. The distillate of arsenic trichloride is then introduced into the Marsh apparatus.

The methods of Gautier (1875) and of Chittenden and Donaldson (1880) are highly commendable when the suggestions of Lockemann are carefully applied. The original methods are unreliable if the oxidation proceeds too violently, with consequent loss of arsenic.

The Neumann (1897) method is based on the same principle as the Gautier method, from which it differs in that the nitric acid

is generated in the mixture, which renders the process more easily manageable.

The method of Igefsky and Nikitin (1900) uses sulphuric acid alone for the destruction of organic material. The Strzyzowski method (1907) destroys the organic matter in the presence of magnesium or calcium oxide, which retains the arsenic during the process of incineration. The Fresenius and von Babo method is well adapted to the systematic search for minerals in general. It utilizes the oxidizing properties of potassium chlorate.

The Reinsch test is valuable when an abundance of material is available. It may be applied directly to a liquid containing organic matter, such as urine, and may be completed in a few minutes. It is based upon the use of copper foil, whereby a stain is produced by the arsenic. The method is applicable in certain cases and in others modification is necessary. Most hydrochloric acid contains small amounts of arsenic. Copper likewise is frequently contaminated with arsenic. Arsenates should be reduced to arsenites with sulphur dioxide and the excess gas expelled. The practical limit of delicacy of this test is placed at 0.0065 mgm. Wormley (1877) claims a delicacy of 0.00065 mgm. The general consensus of opinion is that the method is inferior to the Marsh test.

The Gutzeit test is capable of considerable accuracy provided the organic matter is properly destroyed. However, the question of reagents is one that requires considerable attention. The most disturbing feature of the test is found in selecting paper of the proper absorbing power to be used in selecting standards. The amount of mercury salt absorbed due to variations in thickness of the paper, the lack of uniformity of paper, the degree of moisture in the paper, together with the reagents, have led the authors of this series of articles to adopt the Marsh-Berzelius method. The Gutzeit method is regarded as second to the Marsh method in delicacy and accuracy in determining small amounts of arsenic.

The Marsh test is the most delicate and reliable of the tests for arsenic. Nothing of the original process as described by Marsh remains in the present method of application except the fundamental principles—generation of arsin and its decomposition by heat. Zinc and sulphuric acid or electrolytic hydrogen may be used in liberating the nascent hydrogen used in the process. Electrolytically a regular flow of gas is obtained as long as the current remains uniform. No zinc is required by this procedure. It is to be recommended where there is electric installation. However, the other method—zinc and sulphuric acid—is just as reliable if care and caution are exercised in the selection of the reagents.

In 1914, Myers studied the application of the Marsh method to the determination of arsenic in cerebrospinal fluid following the administration of neosalvarsan (see Barbat, 1915). In order to

place the elimination and retention of arsenic on a more scientific basis it has been apparent that more detail and extensive application have been necessary. To study the chemotherapeutic action of our present-day arsenicals the *frequency of the dose, the stage of the disease, the presence or absence of other complicating pathologic conditions are factors which will determine the conclusions that may be drawn*. The human organism is a vast biologic experiment, and conclusions from an experiment of this kind must be drawn with conservatism resulting from applications to a large number of individuals, thereby eliminating certain idiosyncrasies which at first glance do not become apparent. The study of the elimination of 1 case or even 2 cases would be quite absurd on account of the biologic error which results from diet, disease and amount of liquid used by a patient.

To carry out the investigations and answer the questions which are proposed at the beginning of this paper, it has been necessary as well as wise to review a great deal of the literature. Time and space are not available to point out many of the valuable suggestions that have been useful in carrying out this extensive piece of work. This investigation has been in progress for two years, and in its entirety about two thousand analyses are already involved. The bibliography which is attached will give the casual reader references sufficient to gain a comprehensive idea of the entire subject.

As the result of extensive investigation the Gutzeit and the Marsh-Berzelius methods are found to be most reliable. Preference is expressed in favor of the Marsh modification in that it is believed to be more sensitive in combination with a sufficiently higher degree of accuracy. Myers (1918) described briefly the technique employed. In the present article it has seemed wise to go into details so that any investigator can duplicate these results with the use of average skill and precaution in its application to clinical methods.

*Apparatus.* This laboratory has decided to treat all determinations on the dry basis for the reason that variation in the specific gravity of the specimens—due either to pathologic conditions or abnormalities—has been so large that it was not reliable to depend on volume or weight volume figures. With this view in mind it is desirable to select an analytic balance of a type similar to the one illustrated in Fig. 1, having a guaranteed accuracy of 0.1 mg. A set of weights of corresponding accuracy is desirable.

Porcelain casseroles, analytic balance, analytic weights, specimen tubes, desiccator with calcium chloride, steam water-bath, drying oven, platinum dish, beakers, funnels, filter stand, filter paper, graduated glass-stoppered cylinders (100 cc) and Marsh apparatus are required to carry out these determinations.



*Reagents Required.* All reagents are chemically-pure and free of arsenic. Concentrated nitric acid, concentrated sulphuric acid (special arsenic-free), ferric ammonium sulphate, sodium nitrate, potassium nitrate, standard solution of arsenious oxide, ammonium hydroxide, lead acetate paper, anhydrous calcium chloride (granular), absorbent cotton and distilled water.

All reagents should be examined by the user. Experience has shown that nothing can be taken for granted, and it is on this basis that the present investigation is carried out. When the reagents are found satisfactory it is advisable to order the entire stock of material which is to be used throughout the entire investigation. The arsphenamin products

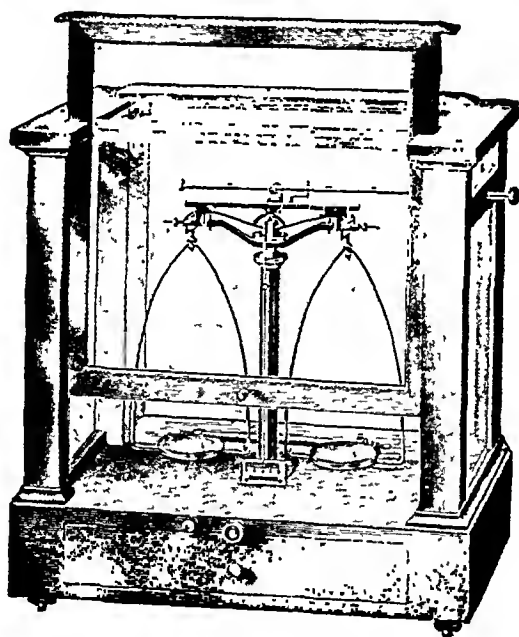


FIG. 1.—Analytical balance with accuracy of 0.1 mg.

used in these experiments are identical in arsenic content, trypanocidal activity and source of manufacture, so that all variations of every kind, with the exception of those due to analytic errors or those involved in the biologic economy are eliminated.

Porcelain casseroles of good quality serve as a convenient type of container. They are heavy enough that the breakage is small. During the present investigation two out of thirty sets have been broken. They are also remarkably constant in weight. The 50 and 100 cc capacity are found most satisfactory for the type of specimens examined. The number used will be determined largely by the extent of the work and the rapidity of carrying out the determinations. These dishes should be dried to constant

weight in an air oven and stored in a desiccator, as illustrated in Fig. 2, ready for use. The weight of the specimen is accurately obtained by difference.

Royal Berlin porcelain casseroles were found most satisfactory as far as breakage and constancy of weight are concerned. The sizes used in these investigations are known as No. 2 and No. 3.

The dishes and their contents after weighing are placed upon the steam-bath and dried. The containers are then dried in the air oven to constant weight.



FIG. 2.—Section of hood capable of accommodating 70 digestions at one time. Desiccator contains dried specimens at the right. Casseroles on water-bath contain specimens. Air oven at left used for drying specimens to constant weight.

When this procedure is finished the organic material is destroyed by using a mixture of nitric and sulphuric acid, then by means of sodium and potassium nitrate, and finally by fusion at low temperature in the platinum dish. The details will be found under Procedure.

The reagents are all tested by means of the control method and the Marsh method.

*Preparation of Reagents.* The special arsenic-free nitric and sulphuric acids are used in preparing this acid mixture. The acid is prepared by mixing 900 cc of concentrated nitric acid and 100 cc of concentrated sulphuric acid. A large supply of these acids is obtained in the beginning, so that there are no variations due to composition of the reagent.

The solution which is to furnish the iron for absorbing the arsenic is prepared so that each cubic centimeter of solution contains approximately 50 mg. of ferric hydroxide. If 226 gm. of ferric ammonium sulphate are dissolved in water and made up to 1 liter a solution satisfactory for this purpose will be obtained.

The concentrated arsenic-free sulphuric acid is diluted, so that the resulting solution contains about 25 per cent of the concentrated acid. Experience has shown that this concentration gives a very satisfactory evolution of hydrogen.

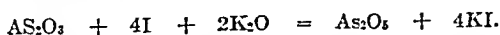
One of the important factors is the careful preparation of the standard arsenic solution which is used in making the standard mirrors illustrated in Fig. 5. A tenth normal solution of arsenic trioxide is used as a starting-point. It contains 4.95 gm. of arsenic trioxide per liter and should be carefully standardized by any of the well-known volumetric or gravimetric procedures. The correction factor must be accurately known, that is, the solution may be a trifle weak, or *vice versa*. This solution is carefully diluted, using volumetric flasks of known calibration, so that each cubic centimeter of solution will contain metallic arsenic equivalent to 0.000001 gm. In other words, if 1, 2, 3, etc., cc of this diluted solution are used the resulting mirrors will contain 0.000001, 0.000002, 0.000003 gm. of metallic arsenic. Sometimes these values are expressed as so many parts per million. In these articles the values are expressed in milligrams of metallic arsenic per 100 gm. of dried specimen.

In order to avoid loss of time in preparing the standard arsenious acid solution the method of preparing it and standardizing it is given in detail together with the principle involved.

"The solution of alkaline arsenite is prepared by dissolving 4.95 gm. of the purest sublimed arsenious oxide in about 250 cc of distilled water in a flask with about 20 gm. of pure sodium carbonate. It is necessary that the acid should be in powder, and the mixture needs warming and shaking for some time in order to complete the solution; when this is accomplished the mixture is diluted somewhat, cooled, then made up to the liter.

"In order to test this solution, 20 cc are put into a beaker with a little starch indicator and the iodine solution allowed to flow in from a burette, graduated in 0.1 cc, until the blue color appears. If exactly 20 cc are required the solution is strictly decinormal; if otherwise the necessary factor must be found for converting it to that strength.

"The principle upon which this method of analysis is based is the fact that when arsenious acid is brought in contact with iodine in the presence of water and free alkali it is converted into arsenic acid, the reaction being:



"The alkali must be in sufficient quantity to combine with the hydriodic acid set free, and it is necessary that it should exist in the state of bicarbonate, as caustic or moncarbonated alkalis interfere with the color of the blue iodide of starch used as indicator.

"If, therefore, a solution of arsenious acid containing starch is

titrated with a solution of iodine in the presence of an alkaline bicarbonate the blue color does not occur until all the arsenious acid is oxidized into arsenic acid. In like manner a standard solution of arsenious acid may be used for the estimation of iodine or other bodies which possess the power of oxidizing it."

Sodium and potassium nitrate solution is prepared by using equal parts of the dry salt and then making a saturated solution.

Dry sodium and potassium nitrate are mixed in equal parts and then ground up to a fine powder in a mortar.

It is quite important at this point to call attention to the fact that this entire investigation has been carried out in a laboratory free from arsenic contamination. All reagents, containers, etc., are new and utilized exclusively for these refined experiments. Manufacturing, laboratory and arsenic treatment rooms are in entirely different buildings.

*Control Experiments.* In order to test the efficacy of the method involving the destruction of the organic matter and the subsequent deposition of the arsenic in the capillary tubes it is necessary to carry out these parallel experiments.

First, it is necessary to establish the purity of the zinc and the sulphuric acid in relation to their possible content of arsenic. Through the courtesy of the New Jersey Zinc Company, Palmerton, Pa., a satisfactory grade of arsenic-free zinc is available. Analyses show that it contains 0.0000002 gm. of arsenic in 100 gm. of zinc. The amount of zinc consumed in an analysis varied between 5 and 10 gm., so that the amount of arsenic in the zinc is very small and is negligible as far as this method is concerned.

Through the coöperation of the J. T. Baker Chemical Company, Phillipsburg, N. J., special arsenic-free sulphuric acid is available. This is diluted so that the solution contains about 1 part of the concentrated acid and 3 parts of water.

The homemade Marsh apparatus consists of a well-made bottle of 300 to 500 cc capacity. Into this bottle a tightly fitting two-hole rubber stopper fits. A 250 cc dropping funnel is used to slowly admit the solution. It is advisable to draw the end of the funnel to a capillary so that the intake of fluid can be easily controlled. The bent tube fits tightly into the other opening of the stopper. In every instance be sure that all connections are tight. About one inch from the lower opening of the exit tube there is a small opening used as a trap to prevent vapors being mechanically carried over into the drying bulbs. In the bend of the tube and in the first bulb, lead acetate paper, cut in strips, is placed for the purpose of absorbing any hydrogen sulphide that may be liberated. The remaining bulbs are loosely filled with granular anhydrous calcium chloride to sufficiently dry the liberated gases. At the end of the tube a small plug of absorbent cotton is placed for the purpose of preventing explosions in case the gas is lighted too soon

before all the air is expelled. By means of a clean rubber connection a piece of Jena hard-glass combustion tubing is attached. This tubing is drawn out to a capillary and all other pieces should be made similarly and of uniform diameter. The portion of the tubing which is to be heated to cherry redness is surrounded by a piece of nichrome gauze, fitting very closely for the following reasons: (a) The heat is distributed around the entire tube; (b) if the pressure of the gas becomes too great the tube while near its melting-point will not blow out. In order to concentrate the heat, pieces of thin asbestos board are placed at each end of the heated area and one above. Heat is obtained from a Meker burner or two well-regulated Bunsen flames.

In order to deposit the metallic arsenic in a definite area a cool stream of water is allowed to slowly flow over the tube as illustrated in Fig. 4. Cold water or iced water is placed in the second dropping funnel and allowed to flow slowly by capillarity over the capillary tube. In this manner the arsenic is collected in a uniform manner and can be easily compared with standard known amounts.

*Precaution.* In solutions contaminated with  $\text{H}_2\text{S}$ ,  $\text{H}_2\text{Se}$ ,  $\text{H}_2\text{T}$ ,  $\text{H}_3\text{P}$ ,  $\text{H}_3\text{Sb}$ , S, zinc sulphide will produce a grayish-white deposit at the place where the arsenic mirror should appear. In carrying out analysis, proper consideration for these possibilities should always be taken into account. Allow the hydrogen to flow for several minutes and then light the gas flowing from the end of the capillary tube. If the light persists and shows no tendency to strike back it is safe to light the larger flames. If this precaution is not observed explosions may follow, much to the danger of other workers, to say nothing about the analyst. Replace the solution in the bottle after each determination. Under ordinary circumstances the lead acetate and the calcium chloride will do for several determinations. A new piece of Jena tubing is necessary for each determination. These tubes can be drawn out several times and then the short pieces may be sealed together, making the expense for tubing a small factor.

Fifty grams of zinc are placed in the bottle of the Marsh apparatus illustrated in Fig. 4 and 100 cc of concentrated sulphuric acid diluted, as described under Reagents, are allowed to act upon the zinc with the evolution of hydrogen. The acid is allowed to drop into the bottle slowly. If any arsenic is present it will be hydrogenated and decomposed as it passes through the heated portion of the glass tube. After decomposition the metallic arsenic will be deposited on the cold portion of the tube. The evolution of gas is allowed to continue over a period of several hours, and if no mirror is formed the acid and zinc are considered satisfactory and free from arsenic in the sense that it contains an amount less than the limits of accuracy of the method. The hydrogen gas

should flow at a uniform rate—at most, not too fast to lead to the formation of hydrogen sulphide. This is decomposed in the hot portion of the tube and leads to the deposition of a sulphur film.

A few drops of copper sulphate or platinic ehloride will hasten the evolution of hydrogen in case a delayed reaction takes place when the acid is added to the zinc.

Jena hard-glass combustion tubing, about 7 mm. in diameter, is the only tubing which has given satisfactory results. Pyrex tubing has either shown a deposit or turned brown at the place where the mirror is to be formed. Any tubing will be suitable

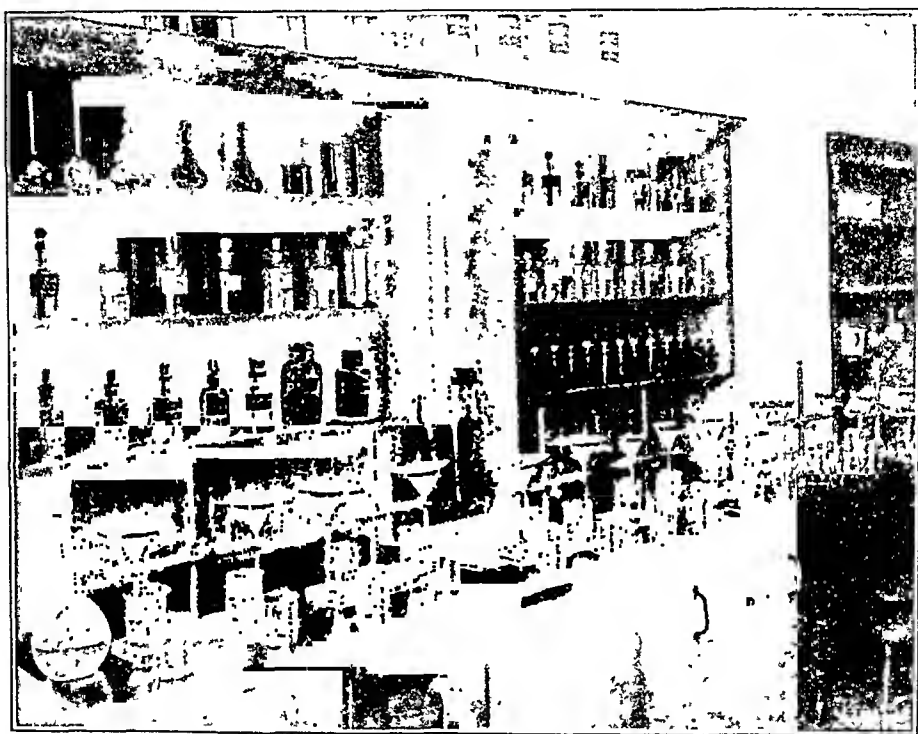


FIG. 3.—Battery of arsenic adsorptions and filtrations just after the specimen has been fused. Twenty or thirty filtrations and adsorptions are carried out simultaneously.

provided it will stand high temperatures, will show no darkening when heated and will give no deposit just beyond the point of heating.

If the evolution of hydrogen is too rapid there will be an escape of arsin which has a garlic-like odor. The arsin is passing through the heated tube so rapidly that it is not decomposed. Amounts of arsin as small as 1 part in 10,000,000 can be detected by its odor.

By this scheme the purity of the sulphuric acid and the zinc is fully established. The next step consists in using the nitrate salts in the same manner as described under Procedure. The solution

is then treated with the iron solution, precipitated with ammonium hydroxide, washed and redissolved. This solution is then run through the Marsh apparatus. The purity of all the reagents will be well established and only one final step remains before the comparisons are made.

In order to test the control method it is necessary to make experiments which are very similar to those by which we examine the blood and other fluids in question: 20 cc portions of normal guinea-pig blood are obtained and placed in porcelain casseroles; 6 of these samples are used in the following manner: Sample No. 1 is used exactly as it has been obtained from the animal while the remaining four samples are added to solutions containing 1, 3, 5, 7 and 10 parts, respectively, per 1,000,000 of arsenic. In this manner we have a blank experiment and five solutions containing different amounts of arsenic. At least four sets of these experiments were carried out in order to test the method which was to be used. By carrying out these experiments the method is carefully checked as far as the possibility of loss is concerned. In parallel with these experiments the standard arsenic solution is Marshes and the results compared with those which have gone through the entire process of destruction of organic material.

TABLE I.

Cubic centimeter standard arsenic solution used.	Mirror in parts per 1,000,000 found.	Cubic centimeter standard arsenic solution used with guinea-pig blood.	Mirror in parts per 1,000,000 found.
Blank.	Blank.	Blank.	Blank.
1	1		
2	2		
3	3	3	3+
4	4		
5	5	5	5
6	6		
7	7	7	7
8	8		
9	9		
10	10	10	10—

By repeating this comparison with and without blood it was found that the method checked up very well. The standard mirrors were prepared by using 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 cc of the standard arsenic solution. The Marshing process must be carried on slowly, so that there is no loss of arsenic in the form of arsine.

*Specimens.* In this investigation, urine, blood-clot, serum, spinal fluid, milk, etc., are collected in sterile tubes and placed in the ice-box until used. In no case should decomposition be allowed to take place for the reason that loss of arsenic may result. It has been shown conclusively that microorganisms may cause the liberation of volatile arsenic compounds. Huss (1913) studied 90 organisms and found that 10 of these liberated ethyl arsine. Several

of these types were not identified, but among them were: *Penicillium brevicaulis*, *Aspergillus caudatus*, *Aspergillus clavatus* as well as some actinomyces.

Witthaus (1911), page 583, describes the organisms which may liberate arsenic as follows:

"Gosio found that common moulds growing in the presence of arsenic compounds evolve a volatile substance containing arsenic and having a pronounced garlic-like odor. The action of *Penicillium brevicaulis* was found to be more pronounced in this regard than that of other moulds, and Gosio has based upon it a test for the presence of arsenic which is claimed by some to be more delicate than the chemical tests. Many other moulds, however, behave similarly, *e. g.*, *Mucor mucedo*, *Penicillium glaucum*, *Aspergillus vivens*, etc., and Schmidt has given a list of thirteen varieties of mould which are active in this manner when grown upon sour paste. The discoveries of Gosio have been verified by Abba, Sanger, Morpurgo and Brunner, Schmidt, Baumert, Bode, Abel and Bittenberg, Scholtz and Maasen."

In other words, the specimens were examined under the most favorable circumstances. Every analysis has a distinct clinical history connected with it, thereby giving an accurate correlation of chemical, clinical and serological findings under controlled conditions.

The specimens were all dried under standard conditions, total solids estimated and arsenic determinations made as described under procedure.

**Procedure.** The specimen is carefully transferred and weighed in a porcelain casserole of suitable capacity. The specimen is then dried at low temperature, preferably on a water-bath. It is then dried in the air oven to constant weight. At least 5 cc of spinal fluid, blood and serum should be used, and 25 cc of urine and larger quantities of the other fluids.

The dried specimens are now treated with mixed acid, drop by drop. A rapid addition of acid may cause foaming, spattering and charring, accompanied by a loss of arsenic. If there is no vigorous reaction the casserole and its contents are placed on the water-bath and allowed to digest. If much oil or fat is present the contents may creep up on the side of the dish. Digestion is continued until the specimen has a yellow oily-like appearance. Practice has indicated that the following amounts of acid usually digest the following specimens:

Mixed acid in cc.	Specimen.
5	Spinal fluid
7	Serum
15	Blood
30	Clot
15	Urine



In case the specimen is not properly digested an additional amount of acid is required. To this yellow oily mass a saturated solution of the nitrate mixture is added, an amount equivalent to 15 gm. of the dried salts. Further digestion is carried on until a crystalline mass is obtained by further evaporation on the water-bath. This process continues the oxidation and also provides alkali salts which combine with the arsenic present. This crystalline mass still contains traces of organic matter which is destroyed by fusing 10 gm. of the dry mixed salts in a platinum dish at the lowest temperature possible. The yellow crystalline mass is added

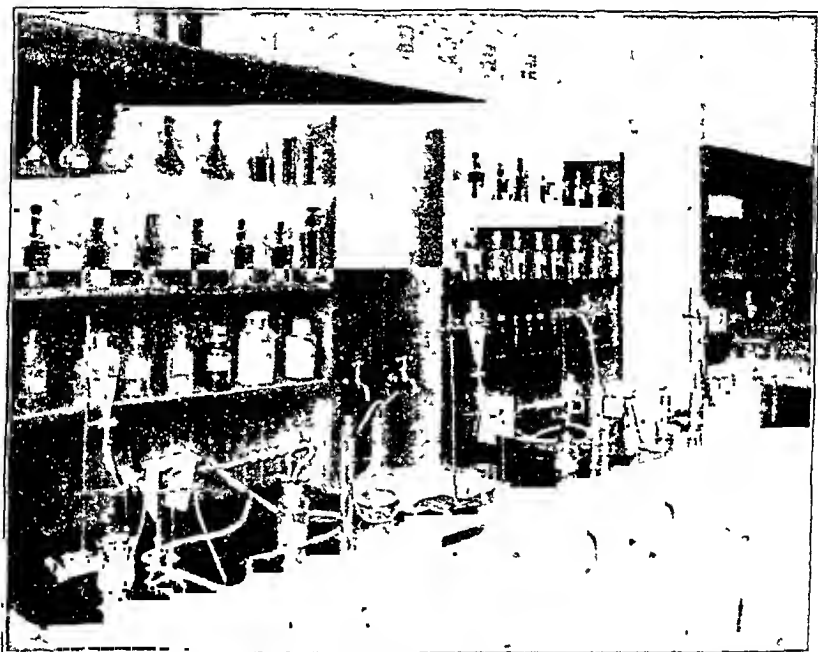


FIG. 4.—Shows Marsh apparatus set up in battery formation. Graduates at the right of each apparatus used to make the volume up to 100 cc. Graduated in cubic centimeters. Each operation handles 6 outfits simultaneously.

slowly to this fused mass by means of a spatula. The whole mass is then fused at a higher temperature with the escape of the nitrous fumes. The porcelain casserole is heated and washed out with 5 cc of concentrated sulphuric acid. When the fused mass has cooled the sulphuric acid is added to the platinum dish and heated gently. There will be a further evolution of nitrous fumes. The fused mass is then dissolved in water and boiled. The contents of the platinum dish are then washed into a beaker of about 300 cc capacity. To this solution the ferric ammonium sulphate is added in amounts corresponding to those in the table. The acid is then partly neutralized. The precipitate of ferric hydroxide

should never be made while the solution is even warm. It must always be done in the cold. The precipitated ferric hydroxide adsorbs the arsenic quantitatively as shown by several authors referred to in the bibliography. The iron-arsenic precipitate is filtered off as illustrated in Fig. 3. The second adsorption is carried out by the addition of more ferric ammonium sulphate to the filtrate, precipitated by ammonium hydroxide and filtered in the same funnel. A third adsorption is carried out in a similar manner by using the second filtrate. The amounts of ferric ammonium sulphate in cubic centimeters used in the three adsorptions for the following specimens are shown below:

Adsorption.	Spinal fluid.	Blood or clot and serum.	Urine.
1 . . . . .	10 cc	15 cc	20 cc
2 . . . . .	5 cc	15 cc	15 cc
3 . . . . .	3 cc	10 cc	10 cc

When all the precipitate has been collected in the funnels the precipitates are washed with distilled water until they are free of nitrates. (Use the ferrous sulphate test on a sample acidulated with sulphuric acid.) After careful washing the iron precipitate is dissolved in 5 cc of concentrated sulphuric acid and made up to 100 cc in graduates shown in the plate with the Marsh apparatus. These solutions will keep indefinitely or until the Marsh test is carried out.

When the Marsh apparatus is working smoothly and the Jena tube is heated to redness the whole solution or an aliquot is allowed to flow in slowly—one drop in every three to five seconds. It is necessary to see that a continuous evolution of hydrogen is maintained.

As a rule it requires about thirty minutes for each Marsh test. In specimens in which considerable arsenic may be suspected it is advisable to use only 5 cc of the solution with 25 cc of water, so that a slow rate of flow will be maintained. If a mirror is obtained with this amount the experiment is completed, otherwise continue adding the solution from the cylinder until a mirror is obtained or the specimen is proved to be arsenic-free.

Quantities as small as one-half part per 1,000,000 are readily detected. The lower range of the scale should be utilized in so far as it is possible. The final calculations are made on the basis of 100 gm. of natural and dry material. The arsenic is expressed in milligrams of metallic arsenic and also in percentage.

In carrying out these experiments, conditions and arrangements are made so that every process is going along simultaneously with those involved with the entire work. All details are given with the intention of carrying out analysis on a large scale.

Fig. 5 shows the range of standard mirrors ranging from the blank to 10 parts per 1,000,000. It is impossible to use this illus-

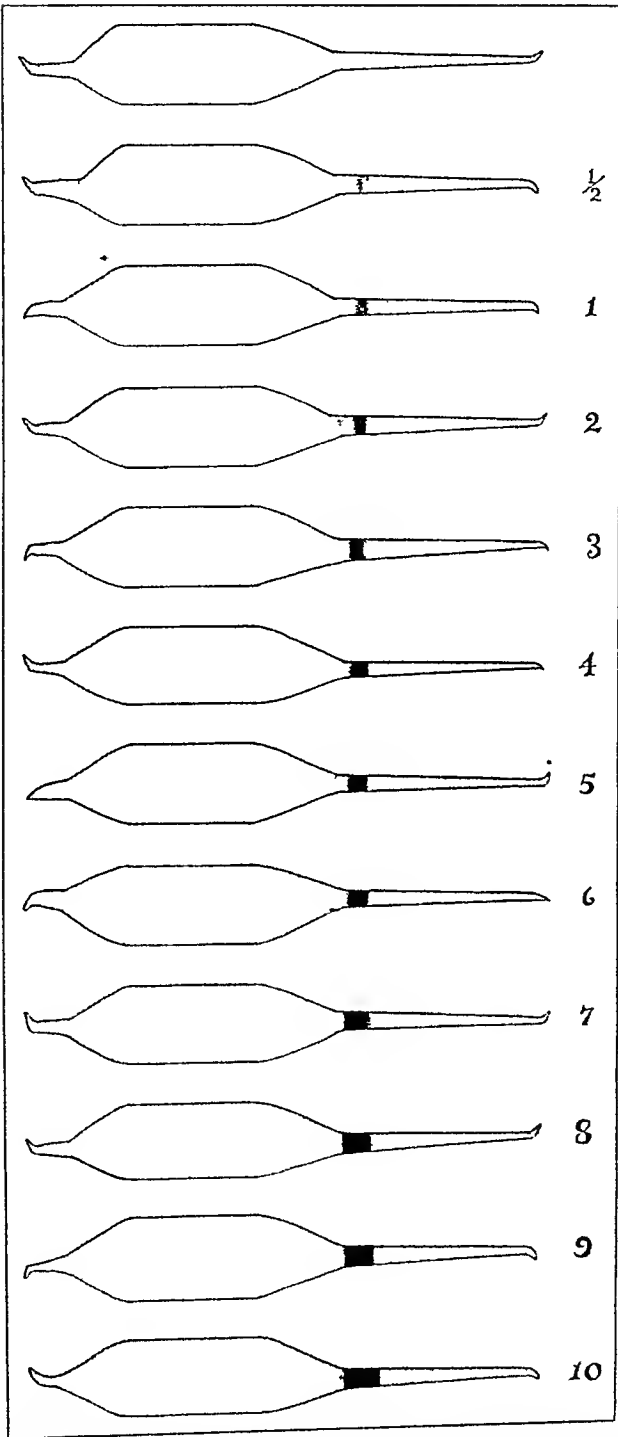


FIG. 5 —Each part indicated in the numerals at the right represents 0.001 mg. of arsenic.

tration for actual comparison in the analytic procedure for the reason that the luster and glass effects must be taken into account. Fig. 5 shows the gradations of readings with very good accuracy. The figures at the right represent parts per 1,000,000, or expressed in milligrams the values are 0.001 mg., etc., when the readings are 1, 2, etc.

The succeeding papers will give detailed information regarding the relation between the clinical and analytic data found.

# BIBLIOGRAPHY.

Aarken, Aaron, and Corper, H. J.: 1916. The Tuberculoecidal Action of Arsenic Compounds and Their Distribution in the Tuberculous Organism, *Jour. Infect. Dis.*, **18**, 335.

Abelin, J.: 1911. Ueber eine neue Methode das Salvarsan nachzuweisen, *München. med. Wehnschr.*, **58**, 1002. Beginn und Dauer der Ausscheidung Salvarsans durch den Urin nach intravenöser Injektion, *München. med. Wehnschr.*, **58**, 1771.

Baccacche, Brunetto: 1913. The Changes in the Biological Properties of the Blood Serum in Phosphorus and Arsenic Poisonings, *Parma. Accad. sci. e lettere Modena*, through *Ztschr. Immunität.*, 11 Teil, Ref. 5, p. 1168.

Bailey, Cameron V., and MacKay, Angus: 1920. Toxic Jaundice in Patients under Antisypilitic Treatment. A Study of the Chemical Analyses of the Blood and Urine and Observations on the Effect of Exercise and Diet in the Treatment of Syphilis, *Arch. Int. Med.*, **25**, 628.

Bang, Ivar: 1916. The Amount of Arsenic in Normal Urine, *Allm. Sv. Lakare-tidn.*, **13**, 549.

1917. Quantitative Determination of Arsenic in Urine, *Farmaceutisk Revy. Schweiz. Apoth. Ztg.*, **55**, 393.

Barbat, J. H.: 1915. Finding of Arsenic in Cerebrospinal Fluid Following Intra-venous Administrations of Neosalvarsan, *California State Jour. Med.*, No. 11, **13**, 415.

1918. Permeability of the Meninges to Arsenic in Paresis and Tabes, *Jour. Am. Med. Assn.*, No. 3, **70**, 147. (See note on p. 148.)

Barthe, M.: 1907. Localization of Arsenic. *Repert. pharm.*, No. 19, **3**, 497.

Beson, Barker, B., and Albrecht, P. G.: 1922. The Elimination of Arsphenamin and Neoarsphenamin in the Urine. A Chemical and Clinical Study of the Abelin Reaction, *Arch. Dermat. and Syph.*, **25**, 51.

Bergman, Hans: 1919. The Storage and Excretion of Arsenic after Administration as Salvarsan in Serum and Water, *Biochem. Ztschr.*, **90**, 348.

Billeter, O.: 1919. Determination of Small Quantities of Arsenic, *Silvetica Chim. Acta.*, **1**, 475.

Bloemendal, W. H.: 1909. Arsenic in the Animal Organism, *Arch. pharm.*, **246**, 599.

Blumenthal, Ferdinand, and Navassart, Emanuel: 1911. Atoxyl Elimination and Distribution of Arsenic after Injection of Atoxyl and Derivatives, *Biochem. Ztschr.*, **32**, 380.

Blyth, Alexander Wynter: *Poisons; Their Effects and Detection, with an Introductory Essay on the Growth of Modern Toxicology.* London: C. Griffin & Co.; New York: Wm. Wood & Co.

Bongrand, J. Charles: 1912. Elimination of Arsenic after Treatment with Organic Compounds of Arsenic, *Bull. Soc. pharm.*, **18**, 152.

Bornstein, A.: 1911. Fate of Arsphenamin in the Body, *Deutsch. med. Wehnschr.*, **37**, 112.

Boswell, Maitland C., and Dickson, J. V.: 1918. The Adsorption of Arsenious Acid by Ferric Hydroxide, *Jour. Am. Chem. Soc.*, **40**, 1793.

Carles, P.: 1917. Arsenic in Sodium Sulphate, *Med. Jour.*, Bordeaux, **88**, 300.

Carlson, C. E.: 1907. On the Different Behavior of Organic and Inorganic Arsenic Compounds toward Reagents and on Their Proof and Their Determination

in the Urine after Introduction into the Organism, *Lund Ztschr. f. physiol. Chem.*, 49, 410.

Chittenden, R. H., and Donaldson, H. H.: 1880. On the Detection and Determination of Arsenic in Organic Matter. I. Method for the Complete Extraction of Arsenic from Organic Matter, *Am. Chem. Jour.*, 2, 236.

Delepine, Sheridan: 1919. Report on Certain Organs in a Case of Fatal Poisoning by Arseniuretted Hydrogen Gas, *Jour. Ind. Hyg.*, 1, 356.

Dercum, F. X.: 1920. Functions of Cerebrospinal Fluid. Spinal Drainage and Intraspinal Injections of Arsphenaminized Serum, *Arch. Neurol. and Psych.*, 3, 230.

Desbourdeauz, Leon: 1920. The Determination of Arsenic and Phosphoric Acids in the Presence of Large Amounts of Salts, *Bull. Soc. pharm.*, 27, 225.

Duret, Paul: 1918. Investigation, Determination and Excretion of Arsenic in the Urine, *Compt. rend. soc. biol.*, 81, 736. A New Method for the Destruction of Organic Matter, *Compt. rend. Soc. de biol.*, 167, 129.

Eichhorst, H.: 1920. Changes in the Liver, Kidneys and Blood Due to Acute Arsenic Poisoning, *Deutsch. Arch. f. klin. Med.*, No. 3 and 4, 131.

Eichler: 1912. Severe Arsenic Poisoning after Salvarsan Infusion, *München. med. Wehnschr.*, 59, 2871.

Ekeley, J. B.: 1913. Distribution of Antemortem Administered Arsenic in Human Cadaver, *Jour. Am. Chem. Soc.*, 5, 483.

Escallon, J.: 1912. The Elimination of "606" in the Urine, *Lyon méd.*, 119, 377.

Evans, B. S.: 1920. A New Process for the Estimation of Arsenic, with Notes on the Chemistry of the Marsh-Berzelius Process, *Analyst*, 45, 8.

Ewins, Arthur, J.: 1916. Estimation of Arsenic in Organic Compounds, *Jour. Chem. Soc.*, 109, 1355.

Fischer and Hoppe, J.: 1909. The Course of Organic Arsenic Preparations in the Human Body, *München. med. Wehnschr.*, 56, 1459.

Foulerton, Alexander, G. R.: 1920. On Poisoning by Arsenobenzol Compounds Used in the Treatment of Syphilis, *British Med. Jour.*, No. 3104, p. 864.

Frankel-Heiden and Navassart, E.: 1913. The Fate of Salvarsan in the Human Body, *Ztschr. f. exper. Path. u. Therap.*, 13, 531.

Freymuth: 1916. Detection of Salvarsan in the Urine, *Apoth. Ztg.*, 31, 387.

Fuehner, H.: 1918. Simple Process for the Estimation of Small Quantities of Arsenic in Corpses, *Berlin pharm. Ges.*, 28, 221.

Fyfe, Andr.: 1852. Ueber die Auffindung des Arseniks, *Jour. f. prakt. Chem.*, 55, 103.

Gabel, G. Otto: 1911. Salvarsan in Forensic Testing, *Arch. Pharm.*, 249, 49. Titration of Salvarsan with Iodine Solution, *Arch. pharm.*, 249, 241.

Ganassini, Domenico: 1920. Behavior in the Marsh Apparatus of Certain Organic Arsenic Compounds Used as Drugs, *Boll. chim. farm.*, 58, 285.

Garnier, L.: 1910. Arsenic in the Liver in Acute Poisoning, *Compt. rend. Soc. de biol.*, 67, 738.

Gautier, A.: 1875. Sur la recherche et dosage de l'arsenic contenu dans les matières animales, *Bull. Soc. d. chim. de Paris*, 24, 250.

1899. The Normal Existence of Arsenic in Animals and its Localization in Certain Organs, *Compt. rend.*, 129, 929.

1920. Normal Arsenic in Living Tissues and Traces of Iodine Found in Air and in Water. Some Necessary Corrections, *Compt. rend. Soc. de biol.*, 170, 261.

Gautier, A., and Clausmann, P.: 1917. Destruction of Tissues for Detection of Arsenic and the Examination of the Ash, *Compt. rend. Soc. de biol.*, 165, 11.

Green, Henry H.: 1918. The Fate of Arsenic after Ingestion by, and Injection into, Live Stock and after Absorption through the Skin in Dipping, *S. African Jour. Sci.*, 11, 72. Note on the Microtitration of Arsenic, *S. African Jour. Sci.*, 14, 518.

Green, Henry H., and Dijkman, Cornelius Derksen: 1919. Some Experiments on the Fate of Arsenic in the Animal Body, *S. African Jour. Sci.*, 15, 640.

Greven, K.: 1910. The Commencement and Duration of the Excretion of Arsenic in the Urine Following Treatment with Ehrlich-Hata Dihydroxy-diaminoarsenobenzene, *München. med. Wehnschr.*, 57, 2084.

Gunn, James A.: 1908. The Action of Arsenic on the Red Blood Corpuscles and a Theory of the Blood Defect in Pernicious Anemia, *British Med. Jour.*, No. 2481, p. 145.

Hall, George W.: 1915. Presence of Arsenic in the Spinal Fluid, *Jour. Am. Med. Assn.*, 64, 1354.

Hall, G. W., Callender, R. W., and Holmblad, E. C.: 1920. Presence of Arsenic in Spinal Fluid, *Arch. Neurol. and Psych.*, 3, 631.

Haller, David A.: 1917. The Treatment of Syphilis of the Central Nervous System. A Comparison of Mercurialized Serum and Salvarsanized Serum, *Arch. Int. Med.*, **19**, 997.

Hamilton, G. R.: 1921. Arsenical Keratosis and Epithelioma, *British Jour. Dermat. and Syph.*, **33**, 15.

Harkins, W. D., and Swain, R. E.: 1909. The Chronic Arsenical Poisoning of Herbivorous Animals, *Jour. Am. Chem. Soc.*, **30**, 928.

Hartman, Willy: 1919. Arsenic. *Ztschr. f. anal. Chem.*, **58**, 148.

Heffter, A.: 1915. The Deposition of Arsenic in the Hair, *Vtjschr. ger. Med.*, **49**, 194.

Heiduschka, A., and Biechy, Th.: 1911. Determination of Arsenic in Urine after the Administration of Salvarsan, *Apoth., Atg.*, **26**, 146.

Hodkin, F. W., and Turner, W. E. S.: 1920. The Discoloration Produced by Lead, Antimony and Arsenic in Lamp-worked Glass Tubing. *Jour. Soc. Glass Tech.*, **4**, 158.

Holland, E. B.: 1916. Detection of Arsenic in Bees, *Jour. Econ. Ent.*, **9**, 364.

Huss, Harold: 1913. Microorganisms Forming Arsin, *Svensk Farm. Tidskrift*, **17**, 265.

Igelsky and Nikitin: Quoted by Scherbacheff, D., 1900. Ueber die Dauer der Ausscheidung des Arsens in gerichtlichehemischer Beziehung, *Vrtlschr. ger. Med.*, **3 F. 19**, 243.

Irokawa, K.: 1914. Excretion of Arsenic in Urine after Subcutaneous or Intravenous Injection of Salvarsan, *Sei-I-Kwai Med. Jour.*, **33**, No. 10.

Jeanselme, E.: 1914. Localization of Arsenic in the Viscera after Injection of Salvarsan, *Presse méd.*, **21**, 857.

Joachimoglu, G.: 1917. The Form in which Arsenic and Arsenious Acids Are Excreted, *Arch. f. exp. Path. u. Pharm.*, **80**, 317.

Jones, E. Gabriel: 1919. British Pharmacopeia Quantitative Limit Test for Arsenic, *Analyst*, **44**, 235.

Kirkby, William: 1918. Marsh's Apparatus, *Pharm. Jour.*, **100**, 286.

Klason, Peter: 1914. Quantitative Determination of Arsenic in Organic Secretions and Compounds, *Arkiv. Kemi. Min. Geol.*, No. 9, 5.

1916. Estimation of Small Quantities of Arsenic, *Arkiv. Kem. Min. Geol.*, No. 5, 6, 1. Determination of Small Amounts of Arsenic and the Normal Content of Urine, *Svensk. Kem. Tidskrift*, **28**, 69; *Arkiv. Kem. Min. Geol.*, **6**, 1.

Kling, Andre: 1917. Arsenical Dextrose, *Ann. Falsif.*, **10**, 438.

Kobert, Rudolf: 1906. *Lehrbuch der Intoxikationen*, Stuttgart-Enke.

Koelsch, F.: 1920. Toxic Action of Arsoniuretted Hydrogen, *Zentralblatt f. Gewerbehygiene*, **8**, 121.

Koetter, Karl: 1914. Investigations on the Excretion of Salvarsan in the Urine after the Intravenous Injection of Concentrated Aqueous and Concentrated Serum Solutions of Salvarsan. Observations on the Influence of Diuresis on the Excretion of Salvarsan, *Med. Klin.*, **10**, 807.

Kohn-Abreast, E., and Bouligaud: 1917. Accidental Presence of Arsenic in Chemical Products and in Some Foods, *Ann. chim. anal.*, **22**, 85, 107, 128, 1920. General Method for the Detection and Determination of Arsenic, *Compt. rend. Soc. de biol.*, **171**, 1179.

Kosian, Wilhelm: 1915. Method for the Determination of Arsenic in Urine, Blood, and Parts of Cadavers, *Pharm. Post.*, **48**, 321.

Kunkel, A. J.: 1905. Beiträge zur Frage des sogenannten normalen Arsens, *Ztschr. f. physiol. Chem.*, **44**, 511.

Kyrle, Josef: 1914. Excretion of Arsenic in the Urine after a Single Subcutaneous Administration of Salvarsan, *Vienna Med. Klin.*, 1914, p. 368; *Zentr. Biochem. Biophys.*, **16**, 650.

Laignel-Lavastine: 1920. Arsenic in General Paralysis, *La médecine*, February, 1920.

Launoy, L.: 1918. Toxicity of Colloidal Arsenic and Arsenic Compounds, *Compt. rend. Soc. de biol.*, **81**, 164.

Lehmann, F.: 1912. Estimation of Arsenic in Salvarsan and Neosalvarsan, *Apoth.-Ztg.*, **27**, 545.

1913. Estimation. II. Examination of Blood and Urine, *Arch. Pharm.*, **251**, 1. Leredde and Rubinstein (see Leredde and Domaine): 1921. *Traitement et prophylaxie de la syphilis*, ed. 2, Paris, Maloine et Fils, Editors, p. 320.

Lewitt, M.: 1917. The Excretion of Salvarsan after Intravenous Injection of Concentrated Solutions, *Deutsch. med. Wchnschr.*, **42**, 518.

- Lillig, R.: 1920. Importance of the Occurrence of Arsenic in the Soil, in Plants, and in the Animal and Human Organism to the Forensic Chemist, *Pharm. Ztg.*, 65, 500.
- Loekemann, George: 1911. Detection of Small Amounts of Arsenic in the Urine Blood, and Other Organic Materials, *Biochem. Ztschr.*, 35, 478. The Absorption of Arsenic by Iron Hydroxide, *Pharm. Zentr.*, 51, 1131.
1913. History of Marsh Test for Arsenic, *Chem. Ztg.*, 36, 1465.
1916. Comparative Investigations on Arsenic Excretion in the Human Urine after Injection of Different Arsenicals (Atoxyl, Arsacotin, Arsenophenyglycin, Salvarsan, Neosalvarsan), *Biochem. Ztschr.*, 78, 1.
- Luehrig, H.: 1909. Interesting Toxicological Cases, *Pharm. Zentr.*, 50, 534.
- Maiye, M.: 1917. Examination of Urine of Syphilitic Patients Treated with Various Preparations of Japanese-made Salvarsan, Hifukwa, Hitsunyodwa Zasshi, 17, 67; *Jap. Med. Lit.*, 2, 5.
- Marshall, J., and Ruan, L. A.: 1909. Is Arsenic Given Off in Gaseous Combination When Putrefactive Changes Occur in Tissues Derived from Animals Poisoned with Arsenic, *Univ. Penna. Med. Bull.*, 22, 180.
- McIntosh, J.: 1914. The Fixation of Arsenic by the Brain after Intravenous Injections of Salvarsan, *Proc. Roy. Soc., London (B)* 88, 320.
- McIntosh, J., and Fildes, P.: 1916. Factors which Govern the Penetration of Arsenic (Salvarsan) and Anilin Dyes into the Brain, *Brain*, 39, 478.
- McNally, William D.: 1917. Retention of Arsenic in the Organs, *Jour. Am. Chem. Soc.*, 39, 826.
- Mees, R. A.: The Nails with Arsenical Polyneuritis.
- Mehrtens, H. S., and McArthur, C. G.: 1919. Arsenic Penetration of the Meninges during the Treatment of Neurosyphilis, *Proc. Soc. Exp. Biol. Med.*, 16, 99.
- Muto, K., and Sanno, Y.: 1912. The Elimination of Arsenic after the Intramuscular Injection of Dihydroxyaminoarsenobenzene, *Therap. Monatsh.*, 25, 599.
- Myers, C. N.: 1916. Arsenic in "Chemically Pure" Zine, U. S. Public Health Reports, 31, No. 40, 2654.
1919. Determination and Distribution of Arsenic in Certain Body Fluids after the Injection of Arsenobenzene, Salvarsan, and Neosalvarsan, U. S. Public Health Reports, 34, No. 24, 881.
- Myers, C. N., and Du Mez, A. G.: 1918. Qualitative and Quantitative Tests for Arsphenamin and Neo-arsphenamin, U. S. Public Health Reports, 33, 1003.
- Neumann, A.: 1897. A Simple Method for the Determination of Phosphoric Acid in Metabolism Experiments, *Arch. f. Anat. u. Physiol. Phys. Abth.*, p. 552.
- New York Medical Journal: 1920. The History of Arsenic, 111, 337.
- Onaka, Marizo: 1911. The Action of Arsenic on the Red Blood Cells, *Ztschr. f. physiol. Chem.*, 70, 433.
- Orfila, M.: 1838. Poisoning by Arsenious Acid, *Bull. de l'Acad. de méd., Paris*, 3, 676.
- Petren, K.: 1919. The Primary Toxicity of Neosalvarsan, *Lancet*, 197, 244.
- Pomaret, M.: 1920. Elimination of Arsphenamins, *Medecine*, No. 2, 2, 123.
- Rabow and Strzyzowski: 1908. Does Arsenic Pass into the Hair after Treatment with Atoxyl? *Therap., Monatsh.*, 22, 197.
- Riebes, E.: 1914. The Absorption of Salvarsan and Neosalvarsan in the Organism, *Arch. f. Derm. u. Syph.*, p. 118, Orig., p. 757.
- Rieger, John B., and Solomon, Harry C.: 1919. Circulation of Arsenic in the Cerebrospinal Fluid, *Jour. Am. Med. Assn.*, 71, 15.
- Rijn, W. van: 1919. Estimation of Small Quantities of Arsenic, *Pharm. Weekblad*, 56, 1072.
- Rogers, L. Joslyn: 1920. Determination of Arsenic in Organic Compounds such as Salvarsan, *Can. Chem. Jour.*, 3, p. 398.
- Romijn, G.: 1917. Pharmacopeia Tests for Arsenic in Drugs, *Pharm. Weekblad*, 54, 1216.
- Rupp, E., and Lehmann, F.: 1911. A Simplified Determination of Arsenic in Atoxyl and Arsacotin, *Apoth. Ztg.*, 26, 203.
- Ryan, Leon A.: 1915. Distribution of Arsenic in Liver Tissue in Cases of Poisoning, *Jour. Am. Chem. Soc.*, 37, 1959.
- Salkowicz, E.: 1909. Arsenic in Urine, *Ztschr. f. physiol. Chem.*, 56, 95.
1916. The Nature of Excreted Arsenious and Arsenic Acids, *Arch. f. exp. u. Path. Pharm.*, 80, 231, 219.
- Seleringa, K.: 1920. Determination of Small Amounts of Arsenic, *Pharm. Weekblad*, 57, 420.

- Schilling and Naumann: 1913. Distribution of Arsenic in the Animal Organism, *Arch. Schiff's- u. Trop. Hyg.*, **16**, 101; *Zentr. f. Biochem. u. Biophys.*, **13**, 125.
- Schmidt, E.: 1917. Arsenic Trisulphide, *Arch. Pharm.*, **255**, 45.
- Schneider, Wien: 1852. Abscheidung des Arsens aus organischen Substanzen, *Arch. Pharm.*, **2 R**, **70**, 40.
- Segale, M.: 1904. Determination of Arsenic in the Normal Tissues by Biological Methods, *Ztschr. f. physiol. Chem.*, **42**, 175.
- Sieburg, Ernest: 1916. Biology of Aromatic Arsenic Compounds, *Ztschr. physiol. Chem.*, **97**, 53. Esters of Aromatic Arsenic Compounds of p-Arsenobenzoic Acid with Amino Acids and Higher Alcohols, *Arch. d. Pharm.*, **254**, 224.
- Sneed, M. C.: 1918. A New Method for the Separation of the Copper Group from the Arsenic Group, with Special Reference to the Identification of Arsenic, *Jour. Am. Chem. Soc.*, **40**, 187.
- Stern, Carl: 1918. The Excretion of Salvarsan after Intravenous Injection of Concentrated Solutions, *Deutsch. med. Wchnschr.*, **42**, 416.
- Strathly, George S., Smith, C. H. V., and Hannah, Beverley, M. B.: 1920. Delayed Arsenical Poisoning, *Lancet*, **198**, 802.
- Strunc, H.: 1908. The Detection of Arsenic by Means of the Marsh Apparatus, *Ztschr. f. anal. Chem.*, **12**, 761.
- Sutton, Francis: A Systematic Handbook of Volumetric Analysis, or The Quantitative Estimation of Chemical Substances by Measure Applied to Liquids, Solids, and Gases. P. Blakiston's Son & Co., Phila.
- Terry, Robert W.: 1919. Arsenic. *Midland Drug*, **53**, 132.
- Ullmann, Karl: Excretion and Retention of Arsphenamin, *Arch. f. Dermat. u. Syph.*, **114**, 511.
- Underhill, P.: 1915. Distribution of Arsenic in the Human Body, *Jour. Biol. Chem.*, **19**, 513.
- Underhill, Frank P., and Davis, Stanton H.: 1922. The Excretion of Arsenic after Serial Administration of Arsphenamin and Neo-arsphenamin, *Arch. Derm. and Syph.*, **5**, 40.
- Uselli, P.: 1913. Elimination of Arsenic by Patients Treated with "606," *Giorn. ital. malatt. vener.*, **53**, No. 2, *Zentr. f. Biochem. u. Biophys.*, **14**, 382.
- Utz: 1920. The Detection of Arsenic in Salvarsan and Neosalvarsan, *Pharm. Zentralhalle*, **61**, 39.
- Venin: 1913. Treatment of Syphilis in the Army with Salvarsan and Related Substances, *Proc. Thirteenth Intern. Med. Cong.*, 1913, Sect. 13, p. 176.
- von Maschka, J.: 1881. *Handbuch der gerichtlichen Medicine.*, **2**, 249; 4 vol., Svo, Tübingen.
- Vuaflart, L.: 1916. Detection of Arsenic by Means of Mercuric Chloride, *Ann. Falsif.*, **9**, 446.
- Warren, W. H.: 1915. Laboratory Manual for the Detection of Poisons and Powerful Drugs (translation, Autenrieth, W.), p. 167.
- Wasiaky, R., and Mayhofer, A.: 1918. Arsenious Acid. *Pharm. Post.*, **51**, 409.
- Webster, John: 1916. Excretion and Secretion of Salvarsan and Neosalvarsan, *Analyst*, **41**, 231.
- Willeox, W. H., and Webster, John: 1916. The Toxicology of Salvarsan, *British Med. Jour.*, No. 1, p. 474.
- Wilson, L. A.: 1918. The Evaluation of Zinc Dust; a Proposed Method of Analysis, *Chem. Met. Eng.*, **19**, 32.
- Witthaus, Rudolph August: 1911. *Manual of Toxicology*, William Wood and Co., New York.
- Wormley, Theodore G.: 1877. Fallacies of Reinsch's Test for Arsenic, *Am. Journ. Med. Sci.*, **74**, 399.
- Zimmermann, W.: 1921. Sensitive Test for the Hydrides of Arsenic, Antimony and Phosphorus by Means of Gold Chloride, *Apoth.-Ztg.*, **36**, 26.
- Zimmern, F.: 1913. Infusion or Injection of Arsphenamin, *München. med. Wchnschr.*, **60**, 1087.



## THE WASSERMANN REACTION IN NON-LUETIC CASES.

BY T. MCKEAN DOWNS, M.D.,

PHILADELPHIA.

(From the Undergraduate Medical Association, Medical School, University of Pennsylvania, and the Laboratories, Philadelphia General Hospital.)

ON December 14, 1920, a young man, aged nineteen years, entered the medical wards of the Pennsylvania Hospital, service of Dr. George W. Norris, suffering from malaria, which he had contracted five months before on the coast of Mexico, while serving in the navy. He had been treated and supposedly cured, and was now suffering from a return of typical symptoms of tertian malaria. His previous medical history was negative. Up until five months previous he had never been ill enough to see a doctor, and he denied venereal history—never any sore on the genitals, no rash, sore-throat, falling of the hair, severe headaches or pains in his bones at any time. His family history was also entirely negative, father and mother living and well, and he never had heard that his mother had had miscarriages.

His physical examination was negative, except for the enlarged spleen characteristic of malaria, a slightly enlarged liver, and a marked pallor. His eyes and teeth were perfectly normal; there were but few palpable lymph nodes; supracondylar glands not felt; no periosteal nodes or bowing of the tibiae; lungs clear; heart normal and genitalia negative.

His blood on admission showed red blood cells, 2,560,000; hemoglobin, 42 per cent, and was loaded with tertian parasites. Urine negative.

He was immediately put upon quinine, 30 gr. per day, and Bland's pills, and at once began to improve.

On December 17, the laboratory reported that the patient's blood Wassermann was weakly positive. Spinal fluid was not examined. On December 21, the patient was discharged, with instructions to take quinin for ninety days, according to Bass's advice<sup>1</sup> and then return to have his Wassermann repeated.

This case caused much discussion as to the significance to be attached to his positive Wassermann. There was an impression among the staff that malaria is frequently associated with a positive reaction, but as no one was definitely sure of this the decision was reached to ignore the Wassermann and treat his malaria, taking up the question of syphilis later. I may say here that he has not appeared since and has been lost track of. Letters to his address are returned by the post-office.

<sup>1</sup> Bass, C. C.: Jour. Oklahoma Medical Association, 1920, 13, 281.

The question thus raised was only partially settled by reference to certain widely used text-books. Osler's *Practice*, edition of 1920, failed to mention the possibility that the Wassermann might be positive in diseases other than syphilis. Schamberg, in his *Dermatology*, edition of 1915, says only "Positive Wassermann reactions may be obtained in yaws, and in a proportion of cases of malaria, leprosy, etc., and within a period of twenty-four to forty-eight hours after the administration of ether."

Osler and Churchman (*Modern Medicine*, 1914) say the reaction is positive in syphilis, tubercular leprosy and fresh malaria; that in other fevers and wasting diseases partial deviation of complement may occur, but these reactions are not truly positive.

Lespinasse<sup>2</sup> says the reaction is not absolutely specific but is considered evidence of syphilis except in yaws, tubercular leprosy, some cases of relapsing fever, malaria during the febrile stage, some cases of experimental trypanosomiasis and beriberi. In all other cases it is impossible to rule out associated syphilis.

Connor<sup>3</sup> says that false positives are known to occur in leprosy, yaws, relapsing fever, malaria during the febrile stage and in diabetes with acidosis.

When the Wassermann reaction was first introduced it was supposed to be specific—to be dependent upon a specific substance in the blood. Subsequent investigation has shown this belief to be fallacious; but though the theory of the test has been impugned, investigation has merely confirmed the belief in its specificity. Its efficiency is very high—all early luetic cases can be detected if several tests are done at short intervals, provided the technic is right. At the same time there have been many reports of cases other than syphilis with a positive reaction. Many of these reports can be accounted for by faulty technic. The test is so complicated, and such meticulous accuracy is required in all its details, that there is a large leeway for error and the human equation. By now the test as done in a good laboratory can be relied on and the results of different men on the same specimen of blood are in most cases consistent, but this degree of efficiency did not always obtain.

There is at present no standardized method generally accepted for conducting the test, and there are nearly as many modifications as there are workers in this field. The wonder therefore is that the test is so very reliable.

The antigens in most non use are the syphilitic, the Noguchi and the cholesterolized—the latter the most sensitive.

The reading of the test is important. The readings usually reported are four-plus, complete inhibition; three-plus, over 75 per cent inhibition; two-plus, 50-75 per cent inhibition; plus,

<sup>2</sup> Tice's *Practice of Medicine*, 1920.

<sup>3</sup> Oxford Loose-leaf *Medicine*, 1921.

25-50 per cent; plus-minus, under 25 per cent; and negative, complete hemolysis. In many cases only four instead of five positive degrees are reported.

These five or six reports may, for all practical purposes, be condensed into three—positive, complete inhibition of hemolysis; negative, complete hemolysis; and doubtful, anything between the two. A positive reaction means syphilis if the few other conditions that are still recognized as giving a positive can be excluded. One single negative standing alone is worthless in excluding lues, but is very valuable confirmatory evidence, and a doubtful reaction must be interpreted by the clinician. It is unjust to any patient to diagnose syphilis by the *Wassermann alone*, unless it shows complete or practically complete hemolysis. In a case known to be luetic, a doubtful (one, two or three plus) reaction is an indication for further treatment.<sup>4</sup>

It is the clinician's business to interpret the test; the laboratory should merely report the behavior of the serum when tested. For this reason Craig thinks it better that the laboratory man should not know the history of the case, lest his reading of the test be biased and erroneous.

There is hardly a disease known in which the Wassermann has not at some time been reported positive, but most often in the other protozoan diseases. So striking used to be the proportion of positives in these cases, that R. Müller, of Vienna,<sup>5</sup> decided that scarlatina could not be a protozoan disease because he so rarely found the Wassermann positive, though he says positives do occur, rarely, in the disease. (I need not say that Müller stands practically alone in this view of the reasons for regarding scarlet fever as non-protozoal in etiology.)

Müller found that in 88 per cent of cases of yaws the Wassermann reaction is positive. He records that the results of different authors in malaria are variable. Bohn, he says, found a positive reaction in 35 per cent of his 46 cases, the reaction disappearing when the malaria was cured.

Bauermann and Wetter (quoted by Müller) using larger material, found only occasionally an incomplete reaction, almost exclusively as the fever was rising. A reaction still positive three days after the disappearance of all fever, in their opinion, signifies lues.

Other non-specific positives are rare. The reasons why they do occur are not known. Müller gives 3 per cent positive in advanced tuberculosis and says that the test is very occasionally positive in various tumors, especially carcinoma, but only when the patient is *in extremis*, with generalized metastases.

Tubercular leprosy shows the large proportion of 19 per cent

<sup>4</sup> See "The Wassermann Test," by C. F. Craig, 1921.

<sup>5</sup> Die Sero-Diagnose der Syphilis, 1913, Vienna.

of positive reactions, but curiously enough, in Müller's experience, the anesthetic form was invariably negative.

Kolmer and Casselman<sup>6</sup> found the Wassermann to be weakly positive in 19 per cent of cases of psoriasis. Of 250 cases of scarlet fever they found none with a positive reaction.

They record 5 cases of malaria; 3 of these had negative reactions; of the other 2, 1 was frankly luetic. The history of the other patient was not obtained. In discussing this paper, Dr. John A. Roddy, of Philadelphia, said that in the Canal Zone, during the summer of 1913, he saw hundreds of cases of malaria on whose serum a Wassermann reaction was performed, with uniformly negative results.

Kolmer<sup>7</sup> says the reaction is highly specific, but is so beset with technical difficulties that much confusion has been caused. Many of the non-specific reactions that have been reported we now know must have been due to technical errors, though false positives undoubtedly occur. Usually there is no difficulty in differential diagnosis. Kolmer finds the reaction often positive in yaws and in leprosy. Positives have been reported in malaria during the febrile stage, but all of his 11 cases were negative. In scarlet fever the reaction is uniformly negative, though the opinion still prevails that the reverse is true.

Anesthesia and pellagra both are occasionally found associated with positive reactions.

The cerebrospinal fluid is much less subject to error than the blood serum. He has found it positive only in cases of yaws and of leprosy in addition to syphilis.

Baermann and Wetter<sup>8</sup> found no positive reaction in 10 cases of malaria.

Michaelis and Lesser<sup>9</sup> found 1 positive reaction in a large series of malaria cases.

Rudolph Buhman<sup>10</sup> found 5 positives in 99 miscellaneous non-luetic cases; 3 of these cases were tuberculous leprosy, the other 2 were tubercular, and later gave a fairly definite history of lues. Included in the list were 15 cases of scarlet fever and 10 of malaria, in all of whom the reaction was negative.

Craig<sup>11</sup> finds false positives with regularity only in yaws, tuberculous leprosy, some cases of relapsing fever, some malarial infections in the febrile stage only, and in some cases of experimental trypanosomiasis in animals. He says that tuberculosis is more commonly associated with syphilis than any other disease and that syphilis of the lung is not infrequently called tuberculosis. If syphilis

<sup>6</sup> Penna. Med. Jour., 1913, 17, 217.

<sup>7</sup> Text-book of Infection, Immunity and Specific Therapy, 1915, p. 465 et seq.

<sup>8</sup> Wien. klin. Wehnschr., 1908, 21, 1765.

<sup>9</sup> Berl. klin. Wehnschr., 1908, 45, 301.

<sup>10</sup> Tr. Am. Gyn. Soc., 1916, 41, 319.

<sup>11</sup> Loc. cit.

be excluded, tuberculosis does not give a positive reaction. If the positive Wassermann in malaria persists after the disappearance of all fever, syphilis is a complication in the opinion of Craig and other observers.

Anesthetic leprosy is never positive; even in the nodular form it is difficult to be dogmatic, for this disease occurs almost exclusively among savage or uncivilized races, which are so thoroughly permeated with syphilis that to exclude it is very difficult in any given case.

A large percentage of positives in non-luetic conditions, in Craig's opinion, means faulty technic in the laboratory.

In 2643 non-luetic cases on whom the test was performed by this observer,<sup>12</sup> only 11 positives were found, 0.4 per cent. Four of these cases had malaria and the reaction disappeared with the fever. The other cases were divided as follows: tuberculosis 3; pityriasis rosea, 3; diagnosis not made, 1. Two of the tuberculous patients later gave suspicious histories and cleared up under anti-specific treatment.

M. O. Biggs,<sup>13</sup> reports 10 cases of "thyroidogenous psychosis," with varied mental symptoms and the ordinary symptoms of Graves's disease. In no case was there any evidence of lues either on physical examination or in the personal or family history. In every case the blood Wassermann was more or less strongly positive. None of these patients were operated upon nor was spinal fluid Wassermann done.

He reports 1 more case, not insane, a woman with Graves's disease of rather severe degree, of twenty-five years' standing. Her history and physical examination were entirely negative; Wassermann was positive at the time of operation. The operation was entirely successful. One year later the patient was symptom-free and her Wassermann was negative. No antiluetic treatment had been taken.

Jean Golay<sup>14</sup> gives the results of his experience in the following table:

Diagnosis.	No. of Specimens.	Negative.	Positive.
Health . . . . .	13	13	
Scarlatina . . . . .	19	18	1 weakly positive
Tuberculosis . . . . .	13	12	1 weakly positive
Neoplasms . . . . .	9	9	
Diabetes . . . . .	1	1	
Pneumonia . . . . .	2	2	
Icterus . . . . .	3	1	2 weakly positive

A. Tourainc<sup>15</sup> says that the reaction is usually positive in spirochetal and trypanosomal diseases. In chronic malaria he finds

<sup>12</sup> Craig, C. F.: *AM. JOUR. MED. SC.*, 1915, 149, 41.

<sup>13</sup> *Jour. Missouri Medical Association*, 1919, 16, 326.

<sup>14</sup> *Internat. Clinics*, 1920, 4, 79.

<sup>15</sup> *Rev. de Méd.*, 1920, 37, 103.

it always negative. In the acute form he very often finds it positive during the rise of the fever (202 cases out of 326) subsequently becoming negative.

He considers the reaction to be not infrequently positive in acute fevers in general, disappearing with the fever. In chronic infections—tuberculosis and leprosy—it is much less frequent. He says the reaction is often positive after anesthesia with ether and especially with chloroform, but never after nitrous oxide.

In the Hospital of the University of Pennsylvania, between 1906 (when the Wassermann reaction was first reported) and February, 1921, 75 cases of malaria occurred, but not until 1916 was a Wassermann done routinely on all cases. The earlier tests were done only where the history was suspicious or the diagnosis for a time in doubt. Twenty-one tests in all were done on malaria patients, but only 8 of these were routine.

Of these 21 cases the Wassermann was negative in 12, of which 3 were routine. In 6 cases the reaction was positive, in the presence of either a frank venereal history, or one strongly suspicious, *e. g.*, admission of gonorrhea, multiple miscarriages in wife, generalized adenopathy, etc. One case had a doubtful reaction with negative history; 1 other with suspicious history had anticomplementary serum and the test was not interpreted. This patient, however, was consideredluetie at the time and a later Wassermann was positive outside. In only 1 case of the 21 tested was there a completely negativeluetie history, with a weakly positive reaction. Concerning this patient, a young colored girl, Dr. George V. Janvier, of Lansdowne, Pa., her physician, reports that he has not seen her since she entered the hospital, and he knows nothing of her subsequent history.

In no case was the reaction repeated in the hospital, even in the probably syphilitic cases, nor is there any record of the time in the malarial cycle when blood was drawn for the test. It would be very interesting and important to know this in the 2 cases with positive reactions and negative histories, but there is at present no way of finding this out.

In the Philadelphia General Hospital since 1910 there have been a total of 154 cases of malaria. Here, also, the Wassermann was not done as a routine measure but only in suspicious cases. In fact, 130 of the 154 cases were *not* tested. Of the remaining 24 the reaction was negative in 15, and 9 cases were either franklyluetie or lues could not be excluded. Here, also, the reaction was not repeated in the hospital and no record was made of the time in the malarial cycle when blood was drawn.

In the Pennsylvania Hospital from 1910 to the end of 1920 there have been 232 cases of malaria, of which only 27 were subjected to the Wassermann reaction. Of these 20 were negative, 6 were positive, but lues was not excluded. One case showed a false

positive. This is the only case I have seen in which the time of drawing blood could be established and where the reaction was repeated with negative results.

CASE—J. F., admitted to the Pennsylvania Hospital August 30, 1914, suffering with malaria: Venereal history negative—denied venereal and the physical examination was likewise negative. He had a chill August 30, the day of admission, and one the next day, but none thereafter. On September 1 his Wassermann was reported positive on blood that was therefore taken either during or very shortly after a chill. He was discharged very much improved on September 4, and his second Wassermann was reported negative on September 5, the next day. It seems likely that blood for this test was taken on September 4—or at any rate long enough after his last chill for the malaria to have ceased to influence his serum.

To summarize, 461 cases of malaria have been examined; 73 of these, or 16 per cent, were subjected to the Wassermann test. Of these 73, 23, or 32 per cent, were positive, with lues not satisfactorily excluded; 47, or 65 per cent, were negative, and 3, or 4 per cent, showed a positive reaction, when lues could definitely be ruled out, as far as history and physical examination will allow.

These figures are inconclusive, though as far as they go they are in accordance with those given by various authors quoted above, with the exception of Touraine, who found the elevated proportion of 202 positives out of 326 malaria patients tested. I cannot explain his results other than by assuming that he was not careful to exclude lues or that his laboratory was at fault. However, to speak definitely, we should have to know what the reaction was in those 389 cases I report who were not tested.

Tuberculosis. The last 500 cases of tuberculosis occurring in the Philadelphia General Hospital were studied. The great majority of these were severe and far advanced cases, for the incipient cases rarely come to this hospital. Here, also, the great majority of the cases were not tested—only 179 tests or a little over 35 per cent; the reaction was more often done here when the physical examination and history were negative than in the malaria cases.

Of the 179 cases in which the reaction was tested, 38, or 20 per cent, were either frankly luetic or lues was not excluded to my satisfaction; 135, or 76 per cent, were negative, and 6, or 45 per cent, had a reaction more or less strongly positive, in the presence of a negative history and physical examination. I append abstract histories of these 6 cases:

1. W. E., severely ill with pulmonary tuberculosis. History and physical examination negative for lues. Sputum positive for tuberculosis.

Wassermann: Cholesterinized antigen, double plus; Noguchi antigen, plus; luetic antigen, plus.

No antiluetic treatment; later all antigens negative.

Patient died of tuberculosis June 23, 1920. No autopsy.

2. J. C., admitted with advanced pulmonary tuberculosis. History and physical examination negative for lues. Sputum positive for tuberculosis.

Wassermann: Cholesterinized antigen, plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died August 9, 1920. No autopsy.

3. F. P., admitted with advanced pulmonary tuberculosis. History and physical examination negative for lues. Sputum positive for tuberculosis.

Wassermann: Cholesterinized antigen, plus; Noguchi antigen, negative; luetic antigen, negative.

Subsequently repeated with same result.

Died August 29, 1920. No autopsy.

4. A. S., admitted with advanced tuberculosis. History and physical examination negative for lues. Sputum positive for tuberculosis.

Wassermann: Cholesterinized antigen, plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died September 18, 1920. No autopsy.

5. Anna S., admitted with advanced pulmonary tuberculosis. History and physical examination negative for lues. Sputum positive for tuberculosis.

Wassermann: Cholesterinized antigen, double plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died September 17, 1920. No autopsy.

6. C. H., admitted with acute tuberculous pneumonia, gravely ill. History and physical examination negative for lues. Sputum filled with tubercle bacilli.

Wassermann: Cholesterinized antigen, double plus; Noguchi antigen, negative; luetic antigen, negative.

Not repeated.

Died December 18, 1920. Autopsy confirmed antemortem diagnosis, and showed many other tuberculous lesions as well, but no evidence of lues, either grossly or on microscopic examination.



It will be noted that in all these cases three antigens were employed. In 5 of these cases the cholesterinized antigen alone was positive; only once did the other antigens react positively also. Of course it is impossible to speak dogmatically from only 6 cases, but this seems to show a hypersensitiveness on the part of this antigen that would detract somewhat from its value in diagnosis. It was indeed remarkable in looking over the hospital records to see how often the cholesterinized antigen would be strongly positive while the other two were either weakly positive or negative.

*Hyperthyroidism.* A study of the cases of hyperthyroidism and exophthalmic goiter cases in the Philadelphia General Hospital and University Hospital was made, but it was found that the Wassermann was so seldom done on these cases in the Philadelphia Hospital and in the surgical wards of the University that nothing was revealed. The same was true of the medical wards of the University before 1915.

After 1915 there were a total of 90 cases of Graves's disease and hyperthyroidism in the medical wards of the University. Of these, 1 (1.1 per cent) had frank lues and 38 (42.2 per cent) were not tested. The remaining 51 (56.6 per cent) cases had negative Wassermans. A total of 13 tests were also done in the surgical wards and at the Philadelphia General Hospital, and these 13 were also negative. In only 1 case of 103 examined was a positive Wassermann found, and that patient had definite lues.

This is contrary to the statement of Biggs above, but I believe is in line with the experience of others.

Drs. D. J. McCarthy, C. H. Frazier and George W. Norris, all of Philadelphia, inform me that in their very extensive experiences with hyperthyroidism they have not met with any cases associated with a positive Wassermann.

It is proverbially impossible to prove a negative, but in Philadelphia at least the proportion of positive Wassermans in hyperthyroid cases seems to be much less than in the general run of unselected hospital admissions. The small number of cases I present shows no evidence that hyperthyroidism stands in any causal relation to the Wassermann reaction.

#### MALARIA.

Wassermann positive and lues excluded.	Wassermann negative.	Wassermann positive and lues not excluded.	Wassermann not done.
3	47	23	388

#### TUBERCULOSIS.

6	135	38	321
---	-----	----	-----

#### EXOPHTHALMIC GOITER.

0	64	1	108
<hr/>	<hr/>	<hr/>	<hr/>

Totals	9	246	62	517
--------	---	-----	----	-----

**Conclusions.** 1. The Wassermann reaction is invariably positive at some time during the course of syphilis, if properly performed, and at sufficiently frequent intervals.

2. It is but rarely positive in non-luetic diseases.

3. It is unusual for it to be positive in malaria. If positive, it is only weakly so (doubtful in Craig's classification) while the fever is rising, becoming negative between paroxysms.

4. It is rarely positive in tuberculosis, and when positive the reaction is weak or doubtful (*i. e.*, not diagnostic of lues in the absence of history or signs). I have found it positive only in far-advanced cases shortly before death.

5. It is not positive in uncomplicated hyperthyroidism.

6. The cholesterinized antigen is probably too delicate to be of value alone in diagnosing lues when there is no history or physical evidence of disease. It is invaluable in following the course of known syphilis under treatment, by reason of its delicacy.

I desire to express here my deep gratitude to Dr. Edward B. Krumbhaar, director of laboratories, Philadelphia General Hospital, for his unfailing kindness and great courtesy to a beginner in medicine.

## A FURTHER NOTE UPON A COMPARISON OF THE SACHS-GEORGI AND WASSERMANN REACTIONS IN THE SEROLOGIC DIAGNOSIS OF SYPHILIS.

BY ROBERT A. KILDUFFE, M.D.,

DIRECTOR OF LABORATORIES, PITTSBURGH HOSPITAL; DIRECTOR OF LABORATORIES, MCKEESPORT HOSPITAL; SEROLOGIST, PROVIDENCE HOSPITAL.

(From the Laboratories of the Pittsburgh Hospital.)

IN a former communication<sup>1</sup> a report was made of the results obtained with the Sachs-Georgi reaction in a series of 296 serums simultaneously subjected to the Wassermann test.

At that time, as the result of the observations made and recorded, the conclusion was reached that "A diagnosis of syphilis or conclusions as to treatment cannot be based upon the results of a Sachs-Georgi test with safety and the reaction is not suitable for general use for this purpose."

Since the publication of this report several others appeared both in foreign and American literature. The foreign reports were almost uniformly favorable, while those of American literature, though varying to some extent, were, in the main, corroborative

<sup>1</sup> Kilduffe, R. A.: A Comparison of the Wassermann and Sachs-Georgi Reaction in the Serologic Diagnosis of Syphilis, *Arch. Dermat. and Syph.*, April, 1921, 3, 1, 415.

of the usefulness of the test. Notable among these are the papers of Hull and Faught<sup>2</sup> and Levinson and Peterson.<sup>3</sup>

The former observers, using a modification of the test in which the test serum is used undiluted in amounts of 0.3 cc, found that their modified reaction agreed with the Wassermann in 88 per cent of 296 serums tested by both methods.

Levinson and Peterson, reporting upon 1042 comparative tests using the modification proposed by Mandelbaum,<sup>4</sup> in which the serum is diluted in the proportion of 3 drops to 1 cc of normal saline solution, with the incubation period in the hot-air incubator lengthened to eighteen to twenty-four hours, followed by twenty-four hours at room temperature, found that the two reactions agreed in 92 per cent of the cases tested.

Immediately following the conclusion of the first series published from these laboratories, and in view of the varying results recorded elsewhere, it was thought that perhaps the antigen used had not sufficient delicacy, and a new antigen was thereupon prepared and a new series inaugurated, the results of which are herewith reported.

In the preparation of the antigen the technic as given by Galli-Valeric<sup>5</sup> was adhered to, as it seems to be that used by all investigators publishing their technic. Absolute alcohol was used throughout and Merck's cholesterin for the cholesterinization of the alcoholic extract. Before cholesterinization the alcoholic beef heart was titrated and found to be anticomplementary in 2.5 cc of 1 to 20 dilution and antigenic in 0.04 cc of 1 to 20 dilution. After the addition of the further 200 cc of alcohol and the 1 per cent alcoholic cholesterin solution (13.5 cc) the anticomplementary titration remained the same while the antigenic unit had fallen to 0.1 cc of 1 to 20 dilution, probably because of the further dilution of the extract by the added alcohol. This antigen was then added to a series of known positive and negative serums in order to determine that precipitation would occur in a sufficient number to indicate its availability for use in the test.

A series of 430 serums was then subjected to parallel Wassermann and Sachs-Georgi tests by the following technic:

**Technic of the Tests.** Sachs-Georgi: The antigen prepared and titrated as indicated above was diluted 1 to 5 with sterile salt solution (0.85 per cent), one part of the saline being added slowly with gentle shaking and the remaining four parts added more rapidly, the shaking being continued. The resultant solution was turbid and milky.

<sup>2</sup> The Sachs-Georgi Precipitation Test for Syphilis, Jour. Immunol., November, 1920, 6, 521.

<sup>3</sup> The Sachs-Georgi Reaction for Syphilis, Arch. Dermat. and Syph., March, 1921, 3, 286.

<sup>4</sup> München. med. Wchnschr., 1918, 65, 204, quoted by Levinson and Peterson.

<sup>5</sup> Corr.-Bl. f. schweiz. Aerzte, December 25, 1919, 49, 1978.

**Serums:** The serums used in the series comprised those taken for diagnosis in the wards of the Pittsburgh Hospital; serums taken as a routine in the gynecologic and obstetric services of the hospital, and those of cases handled through the Morals Court, these last being obtained through the coöperation of Dr. A. H. Eggers, County Medical Inspector, Pennsylvania State Department of Health. In this latter group were known syphilitics, suspects and cases under treatment. A sufficient number of normal Wassermann-negative serums were included in the series to serve as an adequate control.

No serum used was over forty-eight hours old, and many were tested within twenty-four hours of their receipt. All were clear, free from blood and inactivated for fifteen minutes at 56° C.

For the test 0.1 cc of serum was placed in a serologic test-tube and 0.9 cc of sterile 0.85 per cent salt solution added, thus giving 1 cc of a 1 to 10 dilution; to which 0.5 cc of the Sachs-Georgi antigen was added and the tubes gently shaken. They were then placed in the hot-air incubator for eighteen to twenty-four hours, a preliminary reading made and then allowed to stand at room temperature for twenty-four hours, after which the final reading was made. A known negative and positive were always included. Readings were made by transmitted light, using a modified agglutinoscope and recorded as follows:

- ++++ Well-marked precipitate plainly discernible.
- +++ Perceptible precipitate not so marked as ++++.
- ++ Perceptible precipitate not so heavy as +++.
- ± Barely discernible trace of precipitate.
- No precipitate.

**Technic of the Wassermann Test.** All serums were submitted to the Wassermann test at the same time by the following technic:

**Sheep Cells:** Sheep bled the day preceding the test, cells washed until free from serum (four to six washings in normal saline) and used in dose of 0.5 cc of a 2.5 per cent suspension.

**Amboceptor:** Glycerinated serum diluted with normal saline according to titer and used in dose of 0.2 cc.

**Complement:** The pooled serum of two to four guinea pigs diluted 1 to 10 with 0.85 per cent salt solution. Each day preceding the main test, complement was titrated against 0.5 cc of 2.5 per cent sheep-cell suspension in the presence of 0.1 cc of amboceptor and the unit read as the smallest amount producing complete hemolysis in one hour in the 38° C. water-bath. Two units were used in the test.

**Antigens:** A triple battery was used for each serum, consisting of cholesterolized (0.4 per cent) extract of human heart; acetone-insoluble lipoids of human heart; and an alcoholic extract of syphilitic fetal liver. The dose was determined by antigenic and anticomplementary titrations, the amount used being always from two to five times the antigenic unit, which amount was always from five to ten times less than the anticomplementary unit.

The Test: Each serum was used in dose of 0.2 cc and the complement in dose of two titrated units of 1 to 10 dilution. Incubation was in an iced water-bath at a temperature of 2° to 4° C. for one hour. At the end of the preliminary incubation the tubes were placed in the 38° C. bath for five minutes and then the cells and amboceptor added and the test reincubated in the 38° C. bath until all controls were hemolyzed.

Antigen, corpuscle, amboceptor, complement and positive and negative controls were always added. The same antigens were used throughout the tests.

Results were recorded according to the degree of fixation obtained with each antigen separately and the strength of the reaction graded accordingly. A serum was looked upon as positive if 50 per cent or over of inhibition of hemolysis occurred with the cholesterol antigen alone, even though the other two antigens were negative as, on the basis of data elsewhere recorded,<sup>6</sup> and as said by Kolmer,<sup>7</sup> "I have learned from experience to place reliance upon results obtained with a properly prepared and titrated cholesterolized extract."

*Results of Comparison of the two Reactions.* A total of 430 cases was subjected to parallel tests as above outlined. Of these 102, or approximately 23 per cent, gave plus-four fixations, the high percentage of positive cases being largely due to the inclusion in the series of the Morals Court serums, in which a high percentage of positive findings was to be expected, which, for the purpose of this investigation, was to be desired.

Of the Wassermann positive cases, as shown in Table I, the Sachs-Georgi was positive in 30 and negative in 72.

TABLE I.—RESULTS WITH WASSERMANN POSITIVE SERUMS.\*

Number of serums.	Sachs-Georgi reaction.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
102	11	5	10	4	72	30	72

\* Includes serums positive with cholesterolized antigens only.

Table II shows the results obtained with 324 Wassermann negative serums in which the Sachs-Georgi reaction gave 32, or approximately 10 per cent of positive results.

<sup>6</sup> Kilduffe, R. A.: Concerning the Specificity of Cholesterolized Antigens in the Serologic Diagnosis of Syphilis, Arch. Dermat. and Syph., May, 1921, 3, 595.

<sup>7</sup> The Serum Diagnosis of Syphilis and Gonorrhea Employing Human Complement, Am. Jour. Syph., October, 1918, 2, 739.

TABLE II.—RESULTS WITH WASSERMANN NEGATIVE SERUMS.

Number of serums.	Sachs-Georgi reaction.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
324	6	18	3	5	292	32	292

Four anticomplementary serums were all positive to the Sachs-Georgi test.

TABLE III.—RESULTS WITH ANTICOMPLEMENTARY SERUMS.

Number of serums.	Sachs-Georgi reaction.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
4	2	1	1	0	0	4	0

In the first series similar results were obtained and, for the purpose of consolidation, the combined results of both series are shown in tabular form.

TABLE IV.—COMBINED RESULTS WITH WASSERMANN POSITIVE SERUMS.\*

Number of serums.	Sachs-Georgi reaction.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
162	15	5	13	14	115	47	115

\* All positive serums, including cholesterin plus only in both series.

TABLE V.—COMBINED RESULTS WITH WASSERMANN NEGATIVE SERUMS.\*

Number of serums.	Sachs-Georgi reaction.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
544	11	18	7	18	490	54	490

\* Includes serums of both series.

TABLE VI.—COMBINED RESULTS WITH ANTICOMPLEMENTARY SERUMS.\*

Number of serums.	Sachs-Georgi reactions.					Sachs-Georgi positive.	Sachs-Georgi negative.
	++++	+++	++	+	—		
20	2	1	1	2	14	6	14

\* Includes serums of both series.

A study of the tables shows that of 162 Wassermann positive serums, 47, or approximately 29 per cent, were positive to the Sachs-Georgi reaction as here performed, and that in 544 negative serums the Sachs-Georgi reaction was also positive in approximately 10 per cent.

Of 20 anticomplementary serums, 6, or approximately 30 per cent, gave positive Sachs-Georgi reactions.

Every effort was made throughout the present series to make the tests strictly parallel and to perform the Sachs-Georgi reactions with great care in view of the variance from the results obtained by other investigators. The results are obvious and indicate either that the conclusions previously drawn may be reaffirmed and looked upon as corroborated or that the Sachs-Georgi reaction was improperly performed. The only deviation from the original technic was the substitution of 1 cc of 1 to 10 dilution for 10 cc of the same dilution (1:10), and it is not felt that this had any appreciable influence upon the results obtained.

**Summary.** The results of 430 parallel Wassermann and Sachs-Georgi reactions are reported and coördinated with a series of 296 previously reported.

**Conclusions.** The following conclusions, previously stated, are reaffirmed upon the basis of the results herewith reported:

1. The Sachs-Georgi test is often difficult to read.
2. The reaction is neither as delicate nor as trustworthy as the Wassermann test.
3. The Sachs-Georgi reaction may be positive with Wassermann negative serums and negative with Wassermann positive serums in relatively high percentage of cases.
4. The number of non-specific reactions is sufficiently high to render the test unreliable as a means of diagnosis.
5. A diagnosis of syphilis, or conclusions as to the results of treatment, cannot be based upon the results of a Sachs-Georgi reaction with safety, and the reaction does not seem suitable for general use for this purpose.

## TREATMENT OF SYPHILIS AMONG THE INSANE.

BY THOMAS B. CHRISTIAN, M.D.

PATHOLOGIST TO THE STATE HOSPITAL AT MORRIS PLAINS, NEW JERSEY.

At the present time among the hospitals for the insane we are receiving our share of syphilitics. According to the cases in this hospital at least 95 per cent belong in the tertiary class or latent types. In a number of state hospitals all the syphilitics are put under antisyphilitic treatment while in a great majority of them they are not treated. The reason for their not being treated is probably due to the fact that many syphilologists contend that latent syphilis cannot or never can be cured, that is in so far as producing a permanent negative Wassermann is concerned. But is this excuse a justifiable one for not using the methods we have for trying to hold in check this disease? It has been and is now the plan of the U. S. P. H. Service and state boards of health to eradicate syphilis, and to encourage this a number of states have enacted laws declaring syphilis a reportable disease and have established free clinics for treatment of the same.

In insane hospitals we have three distinct types of syphilis to deal with: (1) Cases showing a four-plus Wassermann and a negative spinal fluid with no clinical manifestations of syphilis, this constituting the majority class; (2) cases with a positive Wassermann reaction—a negative spinal fluid—but clinical manifestations of syphilis present, and (3) psychosis with syphilis as the etiologic factor—as general paralysis, taboparesis and tabes with psychosis.

At the present time we are treating all cases of syphilis with a four-plus Wassermann with or without clinical manifestations, including a few selected cases of general paralysis.

It has been, and still is, argued by some eminent syphilologists that patients with a positive Wassermann and with no lesions should not be treated. The basis for their belief is that once infected with syphilis a patient carries it with him to his grave. However, I doubt if anyone has followed a single case of syphilitic infection from the initial lesion to his last day to prove the statement of once syphilitic always syphilitic. Ninety-five per cent of our cases of syphilis belong in the tertiary or latent class with no active lesions and no other signs except a positive Wassermann and the mental symptoms of the paretics. Many of them give a history of a previous chancre—some with treatment while others have had no treatment previous to coming to this institution. We also get a number of positive Wassermans and paretics that had negative histories of initial chancres.

The chances of obtaining a negative Wassermann in cases of latent syphilis, even in very old cases, have been shown to be good,



and therefore such patient should be treated regardless of the mental condition, although a negative Wassermann obtained after a few months of treatment does not indicate that a cure has been effected. Syphilis in itself is an entity and must be treated as such. Whether syphilis is associated with a disease either functional or organic it should be treated. It must be treated as syphilis regardless of whether the mental condition is caused by it or not, and it must be treated vigorously.

Many of the cases admitted here are recognized too late for curative treatment, but there is no reason to let it stand and not try to check the onward progress of the disease. In treating such cases I have found many improvements among the patients even though no complete cure was obtained nor expected. These cases of incurable syphilis would probably never have reached us if they had been treated over long periods of time at the beginning of their infection and until the serum Wassermann and spinal fluid Wassermann were negative.

We do not treat cases of general paralysis expecting a cure, but only to ameliorate their symptoms and hold in check the progress of the fatal disease. In such cases we cannot agree with other men who have worked along this line and found cures and improvements. Some time past we treated vigorously a series of paretics, watching the effect upon the mental condition and blood and spinal fluid, but our conclusions resulted in 2 out of 20 slightly mentally improved and 3 showed a paretic gold curve changed to that of a luetic zone curve.

The two slightly improved cases showed a drop of the Wassermanns to two-plus, but the spinal fluid remained four-plus. About 15 cases showed no change in Wassermanns nor clinical improvement. I have had physicians tell me that it has been their experience to see cases of well-pronounced paresis which had remissions of the disease lasting from one to four years, which followed intraspinal injections. I have also seen similar cases which had remissions of the disease which had no antisypilitic treatments. We have also received far-advanced cases of paresis that were treated in other institutions and left improved or cured according to their records when in reality they were in a normal remission that occurs in a number of cases of paresis.

It is not, in my opinion, an invasion of the brain from five to twenty years after the primary sore which suddenly appears with speech disturbances and grandiose ideas to the patient's death from two to three years. The spirochetes are deposited in the cerebral cortex during the period of generalization of the organisms, as in aortitis and visceral syphilis, where they may remain without reactive phenomena or the spirochetes hidden away in the deeper parts of the brain may act in the same way as in other organs. The spirochetes were probably there from the beginning

and a spinal puncture at that time would have shown the condition present with no clinical signs. We have no case here on record which shows a positive blood and negative spinal fluid and showing a number of years later a positive spinal fluid. If the general practitioner wishes to save his patients infected with syphilis from the dreaded disease of paresis he should obtain a spinal-fluid examination upon every case of syphilis he treats.

Fordyce<sup>1</sup> states that neurosyphilis appears first by pathologic findings in the spinal fluid before clinical symptoms appear. That the tissues may harbor the treponema for an indefinite time with little or no evidence of their presence and that the nervous system may be the habitat of the organisms with little or no tissue reaction until a traumatism or some exciting factor stimulates their activity or until sufficient time elapses to permit centers or tracts to be compromised, which then give rise to objective signs and symptoms. Judging from the above every case of paresis we have in this institution would have shown serologic signs of nervous tissue involvement if a spinal examination had been performed at the time of the general dissemination of the spirochetes. It has been and is now the idea of many that it takes ten to twenty years for paresis to develop after the initial infection, which is true if based upon the clinical syndrome of physical and mental symptoms but not true if based upon the serologic findings in the spinal fluid. Substantiating this statement Fordyce<sup>1</sup> quotes a very interesting case as follows: Patient had chancre on October 20, 1919, and on April 9, 1920, the examination of the blood serum was four-plus; spinal fluid showed 22 cells; four-plus globulin, four-plus Wassermann to 0.1 cc and a gold curve of 5555432100, which is a typical serologic syndrome of paresis. None of the mental and physical signs of paresis were present. Judging from the above case the cases of general paralysis we admit here must have had the laboratory picture of paresis from ten to twenty years before admission and a sufficient length of time must pass to produce the clinical picture of paresis. Therefore it would seem highly improbable that after such a length of time the spirochetes have inhabited the body and produced destructive pathology in the brain that intraspinal therapy is not indicated in institutionalized cases. We have discontinued the intraspinal therapy among the paretics, as our cases are too far advanced for treatment, and our previous treatment in this type of cases gave us no encouraging results. The degenerated nervous tissue is entirely too sensitive for taking care of the irritating salvarsanized serum, as we have had several serious reactions following such treatments. Intraspinal therapy is, however, indicated in early selected cases of neurosyphilis as syphilitic meningitis, meningoencephalitis or meningomyelitis, and is a safe procedure if proper technique is used.

<sup>1</sup> AM. JOUR. MED. SC., No. 3, 156, 313.

We treat a few selected cases of paresis with the idea of holding in check the disease by prolonged treatments of salvarsan and mercury. Previous to administering the salvarsan we drain the spinal canal. This is supposed to enable more arsenic to be transmitted to the nervous tissue from the blood by the vascular meninges and choroid plexus. This method is used by a number of syphilologists with the above idea while others claim it has no effect. I have for some time past drained the spinal canal in excited cases and cases in convulsions, and by thus relieving the pressure they have been relieved. Many paretics in the last stages, however, show a decreased pressure of the spinal fluid.

Every patient admitted to this hospital has a blood Wassermann performed and all cases showing positive bloods is subjected a spinal puncture, and in addition spinal punctures are performed in those cases with a negative Wassermann giving a previous history of a positive Wassermann of initial chancre, those with clinical signs of syphilis and those showing suspicious neurologic signs. We have found a number of cases with positive spinal fluids with a persistent negative blood Wassermann. A number of cases of neurosyphilis are detected only by resorting to spinal puncture. Making serologic examinations upon many of the old cases that have been here from ten to twenty years we have discovered a number of interesting cases. The following example will give examples of other cases:

F. S., admitted in 1908, gave a negative family history, negative venereal history and no signs of syphilis. No Wassermann, however, was performed. His mental picture was that of a dementia precox. During the past year his symptoms have been taking on that of a paresis. On October 12, 1921, for the first time a blood and spinal examination was performed and gave a typical serologic syndrome of paresis. His diagnosis was changed to general paralysis. Was this a case of syphilitic psychosis from the beginning or a case of dementia precox with neurosyphilis, later being a mixed case of paresis superimposed upon dementia precox or a case of early paresis from the date of his admission? Is paresis and taboparesis the only form of insanity which we have as a direct cause of syphilis? Why cannot the spirochetes infect other portions of the brain and give a clinical picture entirely different from paresis and simulating other forms of insanity, the causes of which are unknown? This question has been discussed by eminent psychiatrists, and is one we wish to determine in the future.

If more examinations of the spinal fluid were made in general hospitals and private practice I am convinced that many cases would probably never reach institutions for the insane. The activity of a syphilitic process in the central nervous system is indicated earlier, more accurately and a number of times only by

pathologic changes in the spinal fluid, and the activity of syphilis of the nervous system is shown by the globulin test, cell count, Wassermann and gold solution reaction long before mental symptoms or physical signs are present. Failure to recognize the importance of spinal-fluid examinations leads us to overlook many cases of slow-progressing cases of neurosyphilis until the physical signs and mental symptoms are present, and then it is too late for treatment with the expectation of a cure. I see no reason why anyone should wait until advanced degeneration in important organs is present and stand helpless in its presence when by the simple procedure of a spinal puncture this may be averted. And a great number of times it is the physician's fault, as no case should be discharged as cured without a negative spinal fluid as well as a negative blood. I realize the fact that many patients will not submit to a spinal puncture, and I have met with the same hindrances, but after explaining the importance of the procedure the simplicity of the process and no after dangers they will realize they will have nothing to lose and all to gain.

No case of syphilis should be considered cured after a certain number of doses of salvarsan and mercury. Every individual should be treated different, as some cases will obtain a rapid cure, both clinically and serologically, while others must have treatment over a long period of time.

Syphilis is very insidious in its attack on the brain and central nervous system, and our only protection is a continuous follow-up in the after-treatment of its victims. I have seen a number of cases that fall into the hands of so-called syphilologists and have been discharged as cured and terminated in institutions for the insane as a direct result of syphilis. The following case illustrates a number of others:

Mr. M. F., at the age of twenty-five years, contracted syphilis, and during the primary stage was given six intravenous injections of salvarsan followed by twelve of mercury. He cleared up clinically and a Wassermann obtained one month, three months and four months after treatment had been discontinued was negative, but no spinal-fluid examination was performed. He was admitted here a few weeks ago at the age of thirty-seven years, with a clear mental, physical and laboratory picture of general paralysis.

Of course, one cannot say to a certainty that this or other cases here in similar condition would have been cured had the proper treatment been given them years previous to the outbreak of the mental symptoms and physical signs. But we do know that these cases were not treated over prolonged periods and no spinal-fluid examination was performed to determine if intraspinal therapy was indicated, but were pronounced cured after a definite course of treatment, some without a Wassermann, others with one negative

Wassermann, and others with a number of negative Wassermans, but none with a spinal-fluid examination. And as far as the condition of the patient is concerned a serologic cure is far more important. It is a waste of time to treat cases of general paralysis after mental symptoms and physical signs have set in, as we have seen a number of cases treated vigorously by intravenous-spinous and intraventricular, but no results were obtained.

In general the following is the outline of the method of treatment we use in treating syphilis without spinal involvement: Each patient received ten to twelve injections of salvarsan, the dose depending upon the weight and physical condition of the patient. These injections are given weekly with an intramuscular injection of mercury coming midway between the salvarsan treatments. During the treatment a weekly examination of the urine is performed, and if evidence of nephritis is found, blood chemistry and functional tests were performed, and if the function is shown to be impaired, treatment is discontinued until cleared up. Also a weekly Wassermann and Hecht-Gradwohl test is performed to determine the effect of treatment, the Wassermann being quantitative, the results of which I expect to give more in detail in a later paper. At the end of ten to twelve weeks, which gives the patient from ten to twelve injections of salvarsan and mercury, we take the Wassermann, and if found negative wait until the lapse of one month; take another blood test, if negative then do a third after the third month; and if still negative, we perform a spinal puncture; and if this is negative we pronounce the case as temporarily cured. Now after the elapse of one year another blood test is performed, and if still negative the case is serologically cured. If at any time the blood or spinal fluid is found positive, continue treatment. Those with spinal fluids positive should be given intraspinal therapy. This same plan is followed in private cases as well as institutionalized cases.

If necessary a case can be treated from two to three years with mercury, and salvarsan if administered at long periods and carefully watching the kidneys, liver and skin symptoms. Cases requiring a large amount of salvarsan and mercury should be given a diet consisting mostly of eggs and milk, with an occasional hot-pack for elimination. I do not think there is any advantage in the intensive treatment plan in latent and tertiary syphilis. As to cases showing chancres and secondary lesions I agree with Thom<sup>2</sup> when he states, "Unless treated intensively I desire to go on record as saying that syphilis is, in the vast majority of cases, an incurable disease in so far as rendering a positive Wassermann negative, which after all is the only criterion of cure we have."

From our last 700 injections of salvarsan we have had only two severe reactions, both cases recovering. One was a severe exfoliative dermatitis following the tenth weekly injection and the other a severe jaundice following the third injection. Both cases were taken off salvarsan and given mercury, with good results. The case with the exfoliative dermatitis was a parietic, and three weeks after his last injection his blood test was brought from four-plus to negative, although his spinal fluid remained unchanged as well as his mental condition.

How long should antisyphilitic treatment be continued in latent syphilis? It should be continued until the blood and spinal fluid become negative and continue to be negative at least six months after treatment has been discontinued. If toxic symptoms appear during treatment and a distinct nephritis shown by examination of the urine a sufficient rest will clear them up and treatment can be continued. It has been shown by Anderson<sup>3</sup> that although there is a temporary picture of nephritis following salvarsan no permanent damage to the kidneys results. The above statement as to treatment in latent syphilis cannot be followed with a result in all cases. Some cases will become negative, others partly positive and some will have no effect from the treatment, judging from the Wassermann reaction. Charts I, II and III give an example of three types of latent syphilis we are treating, with the effect upon the Wassermann reaction.

CHART I.—LATENT SYPHILIS. DURATION UNKNOWN. FEMALE,  
AGED THIRTY-EIGHT YEARS.

Name—M. J.

Neo-arsphenamin.		Mercury salicylate.		Blood examination.		
Date.	Dose, gram.	Date.	Dose, grains.	Date.	Wassermann.	Hecht- Gradwohl.
June 24, 1921	0.6	Sept. 17, 1921	1	June 22, 1921	++++	++++
July 1, 1921	0.6	Sept. 24, 1921	1	July 1, 1921	++++	++++
July 8, 1921	0.6	Oct. 3, 1921	1	July 15, 1921	++++	++++
July 15, 1921	0.9	Oct. 10, 1921	1	July 29, 1921	++++	++++
July 22, 1921	0.9	Oct. 17, 1921	1½	Aug. 19, 1921	++++	++++
July 29, 1921	0.9	Oct. 24, 1921	1½	Sept. 28, 1921	++++	++++
Aug. 5, 1921	0.9	Oct. 31, 1921	1½	Oct. 6, 1921	++++	++++
Aug. 12, 1921	0.9	Nov. 7, 1921	1½	Oct. 25, 1921	++++	++++
Aug. 19, 1921	0.9	Nov. 14, 1921	2	Nov. 1, 1921	++++	++++
Sept. 14, 1921	0.9	Nov. 21, 1921	2	Nov. 15, 1921	++++	++++
Sept. 21, 1921	0.9	Nov. 28, 1921	2	Nov. 29, 1921	++++	++++
Sept. 28, 1921	0.9					
Oct. 6, 1921	0.9					
Oct. 13, 1921	0.9					
Oct. 20, 1921	0.9					

<sup>3</sup> AM. JOUR. MED. SC., July, 1921, No. 1, 162, 80.

CHART II.—LATENT SYPHILIS. DURATION UNKNOWN. FEMALE,  
AGED THIRTY-TWO YEARS.

Name—F. S.

Neo-arsphenamin.		Mercury salicylate.		Blood examination.		
Date.	Dose, gram.	Date.	Dose, grains.	Date.	Wasser- mann.	Hecht- Gradwohl.
June 10, 1921	0.6	June 14, 1921	1	June 12, 1921	++++	++++
June 17, 1921	0.6	June 21, 1921	1	June 12, 1921	++++	++++
June 24, 1921	0.6	June 28, 1921	1	July 12, 1921	++++	++++
July 1, 1921	0.6	July 4, 1921	1	July 26, 1921	+++	++++
July 8, 1921	0.6	July 12, 1921	1	Aug. 15, 1921	+++	++++
July 15, 1921	0.9	July 19, 1921	1	Sept. 6, 1921	++	+++
July 22, 1921	0.9	July 26, 1921	1½	Sept. 14, 1921	++	+++
July 29, 1921	0.9	Aug. 9, 1921	1½	Sept. 27, 1921	++	+++
Aug. 5, 1921	0.9	Aug. 15, 1921	1½	Oct. 25, 1921	+	++
Aug. 11, 1921	0.9	Aug. 21, 1921	2	Nov. 29, 1921	+	++
Aug. 17, 1921	0.9	Sept. 6, 1921	2			
Aug. 26, 1921	0.9	Sept. 14, 1921	1			
Sept. 2, 1921	0.9	Sept. 20, 1921	1			
Sept. 9, 1921	0.9	Sept. 27, 1921	1			
Sept. 16, 1921	0.9					

CHART III.—LATENT SYPHILIS. DURATION UNKNOWN. FEMALE,  
AGED TWENTY-EIGHT YEARS.

Name—N. C.

Neo-arsphenamin.		Mercury salicylate.		Blood examination.		
Date.	Dose, gram.	Date.	Dose, grains.	Date.	Wasser- mann.	Hecht- Gradwohl.
Aug. 9, 1921	0.6	Oct. 3, 1921	1	Aug. 7, 1921	++++	++++
Aug. 16, 1921	0.6	Oct. 10, 1921	1	Aug. 16, 1921	++++	++++
Aug. 23, 1921	0.6	Oct. 17, 1921	1	Aug. 30, 1921	+++	++++
Aug. 30, 1921	0.6	Oct. 24, 1921	1	Sept. 14, 1921	++	++++
Sept. 7, 1921	0.6	Oct. 31, 1921	1½	Sept. 28, 1921	+	+++
Sept. 14, 1921	0.9	Nov. 7, 1921	1½	Oct. 12, 1921	+	++
Sept. 21, 1921	0.9	Nov. 14, 1921	1½	Oct. 19, 1921	Negative	++
Sept. 28, 1921	0.9	Nov. 21, 1921	2	Oct. 26, 1921	Negative	+
Oct. 5, 1921	0.9	Nov. 28, 1921	2	Nov. 9, 1921	Negative	Negative
Oct. 12, 1921	0.9	.....	....	Nov. 30, 1921	Negative	Negative
Oct. 19, 1921	0.9					
Oct. 26, 1921	0.9					
Nov. 2, 1921	0.6					
Nov. 9, 1921	0.6					
Nov. 16, 1921	0.6					

The medical literature is full of the different results which men get with different forms of salvarsan. Some make the statement that you get just as good if not better results and less reactions with the neo-preparation while others say the same about salvarsan.

I have used both and personally can find no difference from the effect upon the Wassermann reaction, although I do think the neo-preparation is more toxic in a number of cases. I am treating a woman at present with salvarsan who complains of no reaction, and after a small dose of neo-salvarsan she complained of intense itching over the body and sick stomach with vomiting, and in order to make sure that it was not caused by some physical condition present at that time, I gave another dose of the neo-salvarsan three weeks later and it had the same reaction. But in most cases there should be no difference between the two if administered and prepared properly. The neo-salvarsan is fast becoming popular, as it is very simple to administer and can be administered now with safety and result in 5 cc of distilled water. The following is the technic I use for salvarsan and neo-salvarsan: Double distilled water is used, the second distillation made in an all glass still. The water is distilled and autoclaved the afternoon before the morning treatments and the morning before the afternoon treatments. A separate flask is used for each patient, each flask containing about 200 cc 0.4 per cent sodium chloride. The flask is stoppered with gauze and capped with tin-foil. For some time past I have been using gauze in the place of cotton stoppers, as this does away with having fine particles of cotton fibers in suspension. Both the salvarsan and neo-salvarsan are given by gravity, the only difference is that more solution is used with salvarsan. For administering a regular glass graduated reservoir of 250 cc capacity is used, the end connected with a piece of rubber tubing, six inches long, to that a glass observation tube, and to that another piece of rubber tubing, eighteen to twenty-four inches long, the end of this connected with a Luer glass adapter. (If new rubber tubing is used, boil in distilled water and let soak overnight and rinse well before using.) I use a platinum needle, gauge 19, length one inch, and with this size I find no trouble in entering all size veins, and it is large enough to permit as rapid flow as one desires by gravity, the speed regulated by raising and lowering the reservoir. Into the reservoir place 100 cc 0.4 per cent sodium chloride solution; remove all air bubbles; apply tourniquet, and the instant blood appears in the glass adapter, release the tourniquet and at the same time let the fluid flow; after from 10 to 20 cc have gone from the reservoir and no tumefaction appears over the site of the injection, you are sure the vein has been entered properly and a good flow established. Now pour the solution of salvarsan or neo-salvarsan into the reservoir. If neo-salvarsan is used do not prepare the solution until you are sure the vein has been entered. I have seen reactions from the neo-salvarsan when it was prepared, and for reasons the vein was not entered and other veins had to be tried, and the time consumed was too long to leave the neo-preparation exposed to the air. When all the solution has passed from the



reservoir and through the observation tube the apparatus is lowered and a small quantity of blood runs back into the glass adapter and the needle immediately removed, at the same time pressing for a few moments over the site of injection to prevent the least amount of backflow from the vein. I see no advantage of using two glass reservoirs with an excess of parts nor the apparatus with the combined syringe attachment. With the above method one can get as rapid a flow as he desires, and there is no reason for forcing the solution into the vein.

The method of preparing patients for treatment is to give a saline laxative the night before and nothing to eat five hours before and five hours after injection. This is the ideal method and should be followed in all cases. But among our cases, due to the shortage of attendants and non-coöperation of the patients, it is not followed except in a few cases. However after administering over 700 doses we have had no effects which can be attributed to not carrying out the above precautions. Each patient is given a physical examination to determine the condition of the heart, bloodvessels, lungs, kidneys and liver. We have several cases of chronic nephritis and arteriosclerosis under treatment, and by carefully regulated dose and examinations of urine and heart we have had no untoward results.

**Summary.** 1. From our experience most cases of latent syphilis are not cured; but arrest in the development of the disease and comfort to the patient occur in a number of cases. The cases which show signs of improvement from a serologic standpoint can only be determined by treating and examining the blood.

2. Our results obtained from treating the syphilitic insane have more than compensated for the time and expense, and it is our plan to continue treatments.

3. It is a matter of individual opinion whether cases of general paralysis confined in institutions for the insane should or should not be treated. We have found no results obtained in such cases.

4. Every case in or out of an institution should have a spinal-fluid examination if the blood is positive.

5. Among 1500 cases examined for syphilis 12.5 per cent showed positive Wassermanns, and from this number of positive cases 26.2 per cent showed signs of neurosyphilis: 17.6 per cent being cases of general paralysis and 8.6 per cent other forms of neurosyphilis. It is to be remembered that the above examinations show the results from latent syphilis, as no case recorded in the above shows clinical signs of syphilis excepting the cases of paresis, and they of course belong in the tertiary stage as neurosyphilis.

6. In conclusion, I wish to emphasize the tremendous importance of the early discovery and proper treatment of syphilis and the examination of spinal fluids, and thus to lessen the number of incurable latent syphilis and neurosyphilis.

## THE ROENTGEN-RAY DIAGNOSIS OF TUBERCULOUS CERVICAL LYMPH GLANDS.\*

BY JOHN MUNN HANFORD, M.D.,

NEW YORK.

IN the course of a study of tuberculosis of the cervical glands the roentgen-ray method of diagnosis has served to differentiate it in some cases from Hodgkin's disease, lymphosarcoma, chronic lymphadenitis, carcinoma and cysts. The method has proved so useful as to appear to warrant a presentation of the findings.

From reading and observation one gains the impression that calcification in tuberculous glands of the neck has failed to attract its full share of attention. (1) It is said or implied by good authorities to be rare. (2) Its usefulness in diagnosis by the roentgen ray deserves emphasis.

In discussing tuberculosis of the superficial or external lymph glands, Holt, in *The Diseases of Infancy and Childhood*, states that "Calcification of the glands in this location is rare." *A Text-book of Pathology*, by MacCallum, in referring to tuberculosis of the lymph glands, fails to mention calcification in connection with the cervical glands, yet mentions it as occurring in tuberculous glands generally. From his text on the various groups one might readily conclude that calcification in the cervical lymph glands was not frequent. Adami and Nicholls in 1911, in *Principles of Pathology*, in discussing tuberculosis of the lymph glands, say, "In long-standing cases the glands . . . may contain calcareous spicules." Several recognized pathologists have recently told the writer that they had rarely seen it; and one said he had never seen it.

To contest these views on the rarity of calcification in tuberculous cervical glands the following evidence is presented:

Incident to a three and a half years' study of this disease, during which time some 200 cases have come under close observation and treatment, roentgen-ray plates of the neck of 40 unselected patients were made; 21, or 52.5 per cent of the forty plates, showed definite areas of increased density corresponding in location to the lesions found on physical examination. These areas of density are distinctly more marked than are the shadows of the soft parts. Indeed, they are almost of the density of bone (Fig. 1). They correspond in location to the enlarged glands, sinuses or cold abscesses. They vary in size from a birdshot to an almond; they may be single or multiple; and in two plates the appearance is that of a large area of fine sand (Fig. 2).

\* Read before the Surgical Section of the New York Academy of Medicine, March 4, 1921.

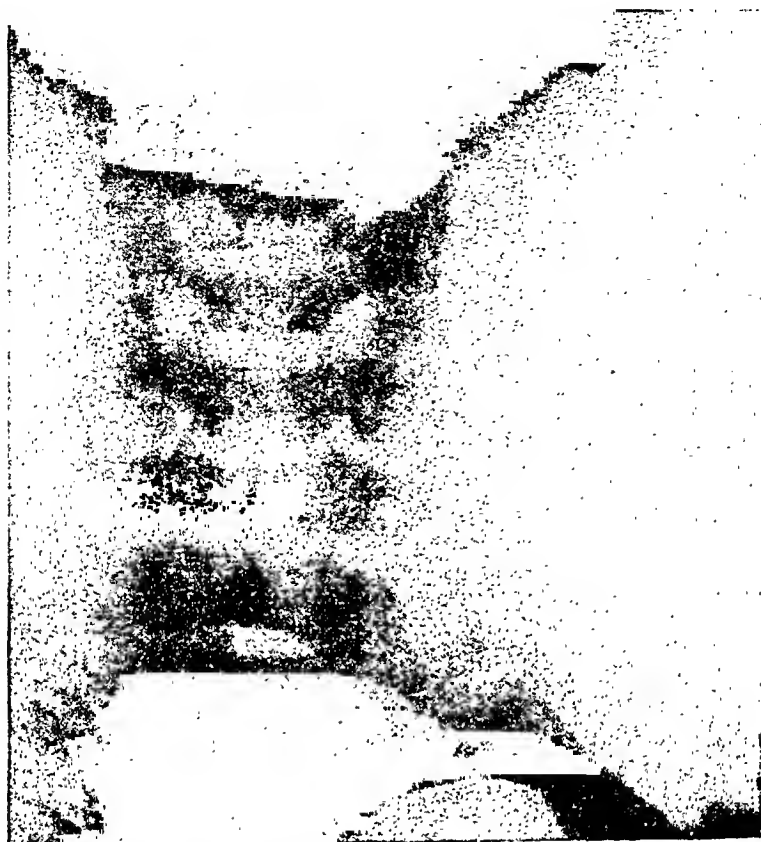


FIG. 1.—A marked example of calcified lymph glands.

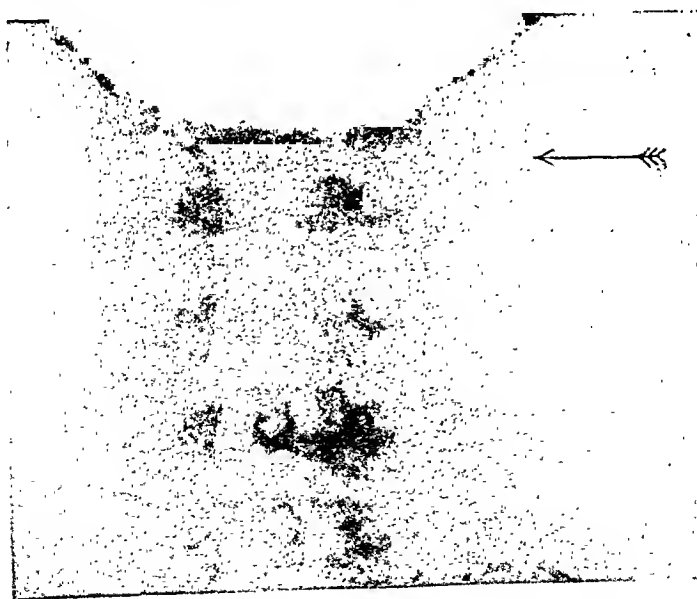


FIG. 2.

Of the 21 patients with positive plates, 10 were proved tuberculous by microscopic examination of tissue excised from the neck. All of the remaining 11 cases were clinically typical of tuberculous glands. Four of these showed such marked, large, discrete areas of density in the plates as to leave little argument about this diagnosis (Figs. 1 and 3). Three were clinically diagnosed in the Presbyterian Hospital tuberculosis clinic as pulmonary tuberculosis (which fact is strong presumptive evidence in favor of the glands being tuberculous). The remaining 4 presented cold abscesses from which typical caseous material was removed and which persisted subsequently as sinuses.

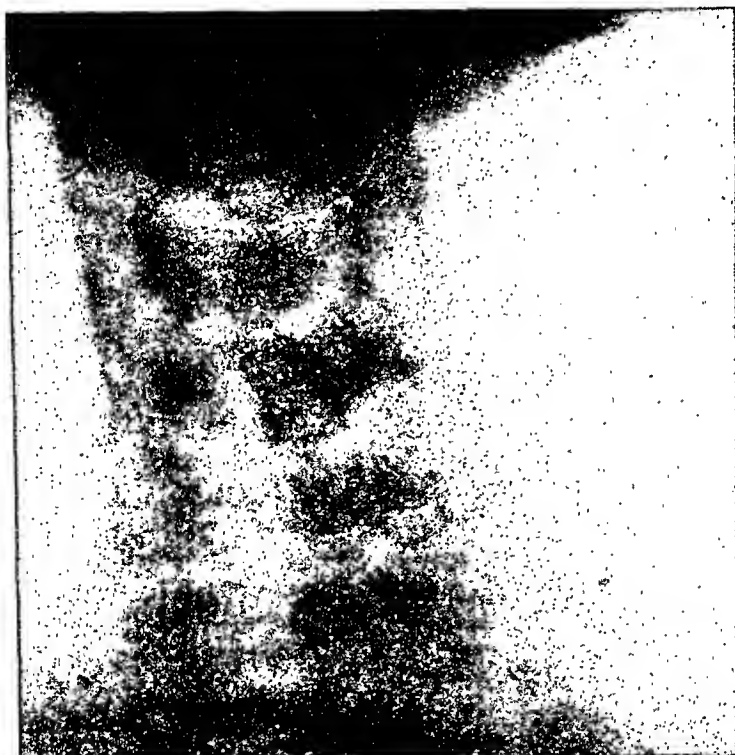


FIG. 3.—This patient had previously had in another hospital by a good surgeon, bilateral "radical" operations, the only patient showing bilateral shadows.

Of the 19 patients who showed no areas of increased density in plates of the neck, 14 were proven tuberculous by microscopic examination or by guinea-pig inoculation. Of the 5 others, 2 had definite pulmonary tuberculosis; 1 presented a cold abscess, caseous material and subsequent persistent sinus; 1 had had proved tuberculous peritonitis; and 1, though not furnishing other evidence, was a typical case clinically. It is the conviction of the writer that all of the 40 patients had tuberculosis of the cervical glands. The age of the patients ranged from five to forty-five years. By chance no younger children were included in the series.

The natural deduction is that the areas of increased density are due to lime salts—to calcification.<sup>1</sup> They have been so reported by the roentgenographic department of the Presbyterian Hospital. Calcification goes with necrosis, and is well known to be common in tuberculosis of the lung and of the mediastinal lymph glands.<sup>2</sup> Tuberculosis of the cervical glands is notorious for its necrosis. What other pathology than calcification incident to tuberculosis could throw these shadows?



FIG. 4.—The lower arrow points to a small shadow corresponding exactly with the site of a small cold abscess. This girl was referred with the probable diagnosis of a branchial cyst.

In this study only a few plates were obtained of non-tuberculous lesions. None showed evidence of calcification. There was one remarkable case of Hodgkin's disease with extensive necrosis and ulceration in the neck of many months' duration which at autopsy showed no evidence of calcification.

In a study of the literature and in a wide personal canvass, simple lymphadenitis, Hodgkin's disease, lymphosarcoma, carcinoma, syphilis, cysts and fistulæ of the neck and other lesions that might be confused with tuberculosis here have not been shown to present calcification nor other changes revealing such increased density by the roentgen ray.<sup>3</sup> It is only fair to state certain exceptions acquired by the writer to this statement. MacCallum

<sup>1</sup> Opie, E. L.: *The Focal Pulmonary Tuberculosis of Children and Adults*, Jour. Exper. Med., June, 1917, 25, 855.

<sup>2</sup> Ibid.

<sup>3</sup> Substantiated by personal communication from Drs. Jobling, Longcope, Symmers Clarke and others.

describes calcification in adenomatous goiter and Le Wald cites instances of thyroid glands showing calcification by the roentgen ray. This would not readily be confused with disease of the lymph glands. In "Notes on Tumors," Wood says, "The contents . . . (of a dermoid cyst) . . . may undergo calcification." These are found, he says, "In the parotid region" and "in the deeper tissues of the lateral aspects of the neck." We know, however, that these locations are rare for dermoids, and we may infer that, even so, they do not frequently calcify. Dr. E. W. Peterson reported to the writer a personal case wherein the pathologist reported calcification in queer malignant tissue from a cervical lymph gland. Calcification of an artery in the neck might throw a confusing shadow, but most of our difficulty of diagnosis in cervical lymph-gland disease we meet in subjects too young for arteriosclerosis.

Four explanations are offered by the writer for the supposed rarity: (1) The lime salts are often thinly distributed in the periphery of the necrotic mass when seen microscopically as a blue layer but not noticeable on gross examination.<sup>4</sup> (2) In 2 of the writer's cases before operation the roentgen ray showed very definite shadows (Fig. 2) while at operation the site of the shadows was occupied by a large cold abscess with a thickened capsule. It is thought that the lime sand was suspended in the pus, like a fine emulsion, and therefore undetected. (3) The pathologists customarily and justifiably examine only one or two of a mass of excised tuberculous glands without searching through the whole. (4) The cervical glands are rarely examined at autopsy.

The 21 positive plates indicate that tuberculous disease of the cervical lymph glands may, beyond all reasonable doubt, give evidence of calcification, and, conversely, that the evidence of calcification, studied in conjunction with the clinical findings, spells tuberculosis.

The practical application of this relatively frequent occurrence at once becomes apparent, and indeed is recognized by individual workers here and there.<sup>5 6</sup> Whatever the percentage of incidence, evidence of calcification is sufficiently frequent in patients with tuberculous lesions in the neck to warrant everyday use of the roentgen ray in diagnosis. It will often save a patient a biopsy which scars the neck, causes discomfort and necessitates some loss of working time.

One plate is so inexpensive as to make it worth a trial even though there is a good chance of its being negative. A small plate that fits between the occiput and the second dorsal vertebra, and snugly against the back of the neck, is more likely to pick up the smaller

<sup>4</sup> Symmers: Personal communication.

<sup>5</sup> Haynes, R. S.: The Differential Diagnosis of Enlargements of the Cervical Lymph Nodes, *Arch. Pediat.*, New York, 1918, 35, 226.

<sup>6</sup> Editorial: Standards of Diagnosis and Treatment of Tuberculous Cervical Adenitis, *Am. Rev. Tuberc.*, Baltimore, 1918-19, 2, 564.

shadows than a larger plate. One anteroposterior view is usually sufficient. The lateral views are rarely helpful, unless there be lesions in the median line, because the glands are largely obscured by vertebræ, mandible, hyoid bone and thyroid cartilage. Except in children the usual chest plate is not long enough to ensure a good view of the chest and the neck.

Evidence of tuberculosis of glands.	21 patients showing shadows in plates.	Age.	Sex.	Number of chart.
Clinical and roentgen-ray plate .	C. S.	30	F.	88307
	G. T.	12	F.	77277
	N. C.	45	F.	97803
	M. M.	48	F.	97958
Clinical and tuberculosis of the lungs . . . . .	L. S.	30	M.	74349
	J. L.	11	F.	96321
	J. M.	26	M.	6947
Clinical, persistent sinus, necrotic material and the old history of excised tuberculous gland . .	T. G.	10	F.	71175
Clinical and persistent sinus . .	K. O'R.	16	F.	92284
	M. S.	6	F.	P. P.
	C. S.	27	M.	1551
Microscopic examination of the tissue excised from the lesion .	E. U.	19	F.	43274
	M. B.	27	M.	46555
	S. P.	30	F.	43444
	E. S.	22	F.	45341
	G. P.	15	F.	48616
	S. T.	10	F.	45771
	H. H.	20	M.	2223
	C. B.	15	F.	1710
	J. M.	20	F.	1737
	H. C.	21	M.	P. P.
19 patients showing no shadows.				
Clinical and proved tuberculosis of the peritoneum . . . . .	J. McK.	10	F.	97662
Clinical and tuberculosis of the lungs . . . . .	A. L.	5	F.	42608
	K. L.	26	F.	97804
Clinical . . . . .	P. M.	28	M.	96052
Clinical and persistent sinus . .	S. G.	23	F.	73387
Microscopic examination of the tissue excised from the lesion or positive guinea-pig test of material from the lesion . . . . .	M. K.	24	F.	92680
	F. K.	24	M.	89999
	M. H.	8	F.	44262
	A. N.	42	F.	35192
	H. Y.	22	M.	37842
	W. F.	23	M.	43265
	T. G.	28	M.	39434
	M. Z.	17	F.	22461
	M. F.	8	F.	93009
	M. R.	14	F.	P. P.
	S. D.	29	M.	2090
	C. W.	28	F.	34232
	F. S.	19	F.	1600
	J. A.	17	M.	49619

It is important to make a positive diagnosis of diseased cervical lymph glands. The treatment varies with the disease. Some cases of Hodgkin's disease and some of tuberculosis profit by therapeutic operative removal; but with a similar clinical picture in each the operation might not be the same. Likewise, and perhaps more important, if roentgen therapy be employed the dosage which, for example, may help to heal tuberculosis may indeed accelerate the advance of carcinoma, lymphosarcoma and Hodgkin's disease.

**Conclusions.** 1. Calcification in tuberculous cervical lymph glands is not rare. Although the series here presented is small, the indication is that calcification occurs in 52.5 per cent of such patients over five years of age.

2. A positive diagnosis of tuberculous cervical glands, abscesses and sinuses may be made so frequently by a small plate, studied with the clinical picture, as to render the roentgen ray worth a trial before subjecting the patient to a biopsy.

The writer acknowledges, with grateful appreciation, the assistance given to this study by the College of Physicians and Surgeons, Columbia University, through the Bull and the Harriman fellowship funds.

### THREE CASES OF LEUKEMIA IN ONE FAMILY.\*

BY CHARLES W. MCGAVRAN, M.D.,

FORMERLY PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF MEDICINE, OHIO STATE UNIVERSITY; PHYSICIAN TO GRANT HOSPITAL, COLUMBUS, OHIO.

THESE cases are reported not because they present unusual clinical features as leukemia, but because of the interesting facts that three members of one family were affected, and of the most unusual combination, there being one of the myelogenous and two of the lymphatic type.

While there are those who hold that leukemia is of bacterial origin and others that it follows infectious processes of long duration, *i. e.*, tuberculosis, syphilis and malaria, and still others that it is due to a new growth of the blood-forming tissues, yet the fact remains that the etiology of leukemia is unknown. We have no evidence that would prove that heredity is a factor in this disease, although some authors have advanced such a theory. Nor has evidence been produced that would cause one to believe that it is transmitted from man to man.

\* Reported to the Columbus Academy of Medicine, November 14, 1921.



Ward<sup>1</sup> has accumulated valuable data as to the familial instance of leukemia, and in his analysis of 1457 cases speaks of Cameron's<sup>2</sup> cases, which were probably acholuric jaundice, and quoting from Ward as abstracted by Tyee, *Practice of Medicine*: "Ward quotes Obrastzow's<sup>3</sup> cases, in which a boy who had acute leukemia was nursed by a male nurse who later developed the same type of leukemia; and Bie's<sup>4</sup> case in which the father of a family died of chronic myeloma, and just before his death a servant girl fell ill of the same disease. Dock's observation<sup>5</sup> of myeloma in a mother whose daughter later developed the same and whose husband developed splenic anemia one year after his wife's death is also referred to."

In the whole series there are two possible instances of familial cases: Jewett<sup>6</sup> had under his care a girl, aged seven months, with acute myeloma. He states: "It seems highly probable from the history that a brother and a sister of this child also died of leukemia. The eldest brother at the age of five months developed enlargement of the abdomen and great anemia. He died six months later. The sister at four months developed marked anemia, splenic tumor and emaciation. She died at eight months. Mother and father are alive and well."

Ward remarks that this report is suspicious on the face of it. Leukemia at so early an age very rarely, if ever, manifests itself first by a splenic tumor, but rather by swollen glands, purpura, etc. These were probably cases of Gaucher's disease. Campbell<sup>7</sup> reported that he knew of a woman under treatment for leukemia whose white cells fell from 400,000 to 5000 after five months' treatment, and adds, 'Her child was under treatment for leukemia at the same time.' There are no further details. Hancsels<sup>8</sup> reports "acute leukemia in a boy whose uncle was also suffering from the disease. The diagnosis appears to have been quite satisfactorily established, but there is nothing to indicate that it was more than a coincidence."

Ward finds that males are more frequently attacked than females and that each of the three forms has an "age of election." Acute leukemia, occurs more frequently up until the twenty-fifth year and has its highest peak during the first five years; chronic myelogenous leukemia is more prevalent between the ages of

<sup>1</sup> Jordon: The Infective Theory of Acute Leukemia, British Jour. Infect. Dis., January-March, 1917, 14, 10.

<sup>2</sup> AM. JOUR. MED. SC., 1888, 95, 28.

<sup>3</sup> Deutsch. med. Wehnschr., 1890, 91, 1150.

<sup>4</sup> Ugeskr. f. Laeger, 1910, 74, 1607.

<sup>5</sup> AM. JOUR. MED. SCI., 1904, 127, 563.

<sup>6</sup> Philadelphia Med. Jour., 1901, 17, 816.

<sup>7</sup> Lancet, 1912, vol. 1, p. 1473.

<sup>8</sup> Wien. klin. Wehnschr., 1908, 21, 594.

twenty-five and forty-five years, while chronic lymphatic leukemia more often occurs between the forty-fifth and sixtieth years.

The cause of leukemia being unknown, no opinion will be ventured as to why three male members of the same family were affected with this disease. The author is fully aware that no case report is complete without an autopsy, and particularly that a diagnosis of leukemia is not complete without the pathologic findings of the blood-forming tissues. Two of these cases were under the observation of the author at the same time, and are reported in detail, showing the clinical work that led to the diagnosis.

On July 6, 1920, S. S. L., aged fifty-nine years, a stonemason, complaining of headache, nausea and vomiting, was seen in consultation with Dr. T.

*Family History.* Father died at eighty-three years of age; mother living, eighty years of age and healthy. There were four brothers—one brother living and healthy at thirty-five; one died at forty of epilepsy; one died at forty of leukemia; one died in childhood, cause unknown. There were five sisters—two are living and well, aged thirty-six and forty respectively; three sisters dead: one died at fifty-eight of tuberculosis, one died at forty-three (cause unknown) and one died at thirty of tuberculosis.

Patient is married (wife is healthy, the mother of four healthy children, and has not miscarried); he has had no previous serious illness. Three years ago he noticed a dry scaly condition on the right side of the face about the size of a nickel. This was diagnosed cancer by Dr. S., who treated it with the roentgen ray every week for a year, but with no improvement. He then consulted Dr. X., who used paste; by this time he had sores on both sides of the face, the lower lobe of the right ear being involved. His face healed promptly after the use of paste, leaving large scars. Since that time until two weeks ago he has been working at his trade. Two weeks ago he began to feel sick, paroxysmal frontal headaches coming specially at night; at about the same time he began to have nausea and vomiting, and has retained little food. His physician found several infected teeth, which have been extracted. His headaches have progressively increased in severity. Today he is delirious.

*Physical Examination.* "Patient is poorly nourished; muscles of good tone. Hair thin and gray; scalp shows considerable seborrhea. Pupils equal, react promptly to light and distance. Mucous membranes somewhat under color. Patient is confused; seems to see all right but cannot answer questions intelligently. Tongue is coated; teeth chewing-surface poor; gums sore from recent extraction; tonsils cryptic and show evidence of infection; large stellate scars on each side of the face; lobe of the right ear is

deformed; all the superficial glands (submaxillary, cervical, post-cervical, axillary and inguinal) are palpable; they vary in size from an acorn to that of a walnut; they are freely movable and not tender; the radial pulses are equal, regular as to force and frequency, of low tension and easily compressible; blood-pressure, 110/68; the chest and vertebral column are negative; heart and lungs show nothing remarkable; examination of the abdomen is quite unsatisfactory, owing to the extreme muscular rigidity and the mental condition of our patient; he not only does not assist in the examination but moves from side to side, making a satisfactory examination impossible; the abdomen is distended; the area of splenic dulness is increased, but its actual size is not determined; the knee-jerks are preserved.

*Discussion.* "A very interesting case and one worthy of complete clinical study. Should the glandular involvement be a metastasis from the face, and if the face lesion was a cancer, the prognosis is hopeless. We must not, however, overlook the possibility of lymphatic leukemia or syphilis. Will examine blood, urine and make a Wassermann."

July 7, 1920. Whites, 162,000; lymphocytes, 95; small lymphocytes predominating cell; only moderate number of smudges.

July 7, 1920. Urine: amber; acid; albumin, very slight trace; sugar negative; microscopic: moderate number of red blood cells with occasional pus cell; no casts.

July 8, 1920. Hemoglobin, 80; reds, 4,000,000; whites, 170,000; smears show the same picture as before.

July 8, 1920. Wassermann negative.

July 8, 1920. Diagnosis of lymphatic leukemia is made. Benzol, gr. seven, in capsules t. i. d., and sodium cacodylate, gr. six, intravenously every third day, were recommended.

July 20, 1920. Reds, 4,100,000; whites, 98,500; blood picture shows no change except fewer cells; reds are normal in appearance.

July 31, 1920. Hemoglobin, 80; reds, 3,520,000; whites, 65,000; polynuclears, 2; lymphocytes, 98.

While there was a reduction in the number of white cells following the administration of benzol and arsenic there was no improvement in the patient; he gradually became more toxic and died during the first week of August. Autopsy, although greatly urged, was absolutely refused.

July 8, patient's son came to the office and was told of the diagnosis and the grave prognosis. Among other things the author said: "While your father's blood count is high, it does not compare with that of the patient who just left the room before you entered. While your father has a leukocyte count of 162,000, that man came here four months ago and we found a leukocyte count of over 300,000." "Why, doctor! that man is my father's uncle."

I. C. L., male; married; aged sixty-nine years, farm superintendent, was first seen February 17, 1920.

*Complaint.* Shortness of breath and precordial pain upon exertion.

*Family History.* Father died at sixty-three of apoplexy; mother died at seventy-one years of age; there were six brothers: one living and well at eighty; five dead—one died at forty-five of epilepsy; one died at fifty of epilepsy; one died at eight-two years of age; one died at seventy-one of heart disease; one died at seventy-six of heart disease. One sister living and well at seventy-seven; one sister died at sixty-eight, cause unknown.

*Present History.* Has been a fairly healthy man. Has never had any serious illness. Has lived a life of exposure. Has been subject to frequent colds. For the past fifteen years has had frequent attacks of "catarrh" of the bowels, manifested by abdominal pain and diarrhea. Prior to six years ago had attacks of severe epigastric colicky pain. For the past three years has had shortness of breath and precordial pain upon exertion, gradually becoming more severe. These pains are precordial and radiate up the sternum and down the arms, especially the left. He at times perspires freely, during and after these attacks, and has a feeling of depression and great anxiety. For the past three years has had more or less ringing in the ears. Has no headache. Vision is not disturbed. Appetite is good; eats everything; now masticates well, although until two years ago he was without teeth for twelve years. Bowels are regular; he is a good sleeper; formerly weighed 155 to 160 pounds, but one year ago lost to about 135 pounds. Today weighs 132½ pounds. Kidneys act freely; nocturia one to three times.

*Physical Examination.* Patient is poorly nourished; muscles of fair tone. Hair gray; scalp in fair condition. Temporal arteries are tortuous; advanced arcus senilis. Pupils equal; react promptly to light and distance. Mucous membranes under color. No marked obstruction to nasal breathing. Tongue is slightly coated; teeth artificial above and below; fauces somewhat injected; tonsils cryptic and show evidence of past inflammation; thyroid negative; the postcervical, axillary, epitrochlear and inguinal glands are distinctly palpable, varying in size from that of a pea to a hickory-nut; they are freely movable and not tender; the larger glands are found in the inguinal region; radial pulses are equal (76), regular as to force and frequency, not of high tension, easily compressible; radial arteries are just palpable; brachials are distinctly palpable and tortuous; blood-pressure, 148/74. Chest is symmetrical; vertebral column negative; decided pulsation in episternal notch; percussion of the chest is negative, cardiac dullness being 11 cm. to the left and 3 cm. to the right of the midsternal line on a level

with the fifth interspace, being 7 cm. at the junction of the third costal cartilage with the sternum. Breath sounds are clear except for many indeterminate rales scattered throughout the chest. Heart tones are clear but metallic. There is a decided cardio-vesicular murmur just over the second left rib. Abdominal examination shows a left inguinal hernia, for which patient is wearing a truss. There is tenderness in the epigastrium. Lower border of the stomach three finger-breadths below the umbilicus—patient in recumbent posture—lower border of liver one finger-breadth below the costal margin; in the midline there is an area of dulness which is probably the liver, extending four finger-breadths below the ensiform appendix. Area of splenic dulness greatly increased. Lower border of spleen distinctly palpable four finger-breadths below the costal margin. Unable to palpate either kidney. The prostate is not specially tender; is hard and nodular.

*Discussion.* The history of this case is quite typical of coronary sclerosis. It is specially interesting in view of the low blood-pressure. The interesting things brought out in the examination are the involvement of superficial glands together with the enlarged spleen and the general prostatic hypertrophy. Will make the complete clinicals.

February 17, 1920. Hemoglobin, 70; reds, 3,380,000; whites, 330,000; differential; polynuclears, 3; lymphocytes, 95; mononuclears, 2. This is a case of lymphoid leukemia. The predominating cell is the small lymphocyte, although there are a few large and intermediate forms; only a few smudges; the reds show no variation of shape or size. They have a slight washed-out appearance.

February 17, 1920. Urine: specific gravity, 1020; sugar, negative; albumin, slight trace; microscopic: very occasional hyaline cast.

February 18, 1920. Urine, twenty-four hour specimen: 700 cc; specific gravity, 1022; albumin, very faint trace; sugar negative; microscopic: no red blood cells; no casts nor pus cells found. Blood: Whites, 378,000; differential same as reported above. Feces: Formed; dark brown in color; occult blood negative; microscopic: shows no undigested meat fibers; no increase in fat; no parasitic ova.

February 18, 1920. *Fluoroscopic Examination of Chest and Abdomen.* Barium meal shows stomach to be normal in position and contour; definition not good; peristalsis normal; duodenal cap shows no irregularity. There are dense areas beneath the diaphragm on both the right and the left of the stomach. Heart shows nothing remarkable. There is an increase of mediastinal tissue, but this is not marked. In six hours the stomach is empty. Head of the meal in ascending colon; in thirty hours the entire colon is visualized and shows nothing remarkable.

February 19, 1920. *Diagnosis.* Lymphatic leukemia with coronary sclerosis and prostatic hypertrophy. The prognosis is not good.

Patient was advised to rest and was given three injections of arsphenamin in 0.3 gm. doses at intervals of two weeks. At first there seemed to be some improvement; the patient said he felt stronger, and the spleen on March 17 was smaller, being 3 cm. below the costal margin. There was only a slight reduction in the white count. Following the third injection of arsphenamin on March 17 there was a severe reaction and the patient reported on April 14, saying that since he was resting he has had no precordial pain, but that he now felt quite weak. He weighed 131 pounds; spleen was larger than when he first presented himself and a definite increase in size of all superficial glands. His blood showed 400,000 whites, over 98 per cent being lymphocytes, the great majority of which were small.

He was then placed on benzol, gtt. vij, in capsules after each meal, and was sent home with a letter to his family physician, Dr. S., advising that he be given sodium cacodylate, gr. iij, intravenously, twice a week.

On May 21 the patient returned, saying he felt much stronger. But other than a reduction in the number of the white cells there was no change in his condition; the count showed 144,000 whites; smear shows the percentage of lymphocytes to be about the same; more smudges than in former slides.

On July 7 examination showed no change clinically; blood: hemoglobin, 75 per cent; whites, 198,000; differential unchanged.

On September 1 the patient says he has been working every day, has had no precordial pain and very little shortness of breath; feels much stronger. Blood: Hemoglobin, 85 per cent; whites, 98,000; differential unchanged. The author's remarks on patient's case record on that date were as follows: "The spleen, liver and superficial glands remain unchanged in size. Patient seems stronger, and as long as he improves under benzol and sodium cacodylate will not recommend radium, although should there be an increase in the number of lymphocytes I will at once advise use of radium."

On November 8 the patient returned, saying he felt better, although two weeks before he had a severe attack of neuralgia of the heart, lasting over three hours and requiring a hypodermic of morphin (this was angina). He looks more pale, otherwise no change in his condition. Weight today, 124½ pounds. Blood: Hemoglobin, 75 per cent; reds, 2,500,000; whites, 54,000; smear shows about the same differential, a thin smear giving many smudges; red cells show no irregularities as to shape and size.

It is to be noted that while the patient thinks he is better, the

only change that might be considered as an improvement is the reduction in the number of lymphocytes, in which there has been a notable drop. On the other hand he is more anemic and continues to lose in weight.

A letter from Dr. S., stated that on November 13 the patient became toxic and died on November 20, and that no autopsy had been held.

The son then said, "Five years ago my uncle, W. G. L., died of some blood disease; he was treated by Dr. H. M. Brundage."

Dr. Brundage reports as follows: "I examined my records carefully and can only find the enclosed blood count in the case of Mr. W. G. L. I saw him at the request of Dr. H. The blood count, you will notice, is significant of splenomyelogenous leukemia. I gave him every possible treatment from benzol to the roentgen ray, and even salvarsan was administered. He requested that at his death I should make a postmortem, which, as I remember, did not reveal anything extraordinary outside of a very large spleen."

Clinical report of Dr. Brundage: "Hemoglobin, 78; erythrocytes, 4,616,000; leukocytes, 213,000; polynuclears, 55; small lymphocytes, 4; large lymphocytes, 3; mast cells, 4; neutrophilic myelocytes, 33; eosin, 1.

H. M. BRUNDAGE, M.D."

Our great regret is that an autopsy in the case of S. C. L. was absolutely refused. In view of the lack of pathologic evidence these cases are reported at length in order to strengthen the claim of a diagnosis of leukemia.

W. G. L., as reported by Dr. B., and who died of myelogenous leukemia, and S. C. L., who died of lymphatic leukemia, were brothers, and I. C. L., who also died of lymphatic leukemia, was their uncle, being their father's brother.

This family has certainly been "hard hit," for you will observe that in addition to the leukemia there were 3 cases of epilepsy, 2 in the branch I. C. L. and 1 in that of S. S. L. There were also 2 known deaths from tuberculosis in the branch of S. S. L. and 1 doubtful case in the family of I. C. L.

The author does not wish to be understood as trying to strengthen the claim of heredity as a factor in leukemia. He has endeavored to establish the diagnosis of leukemia and to report these cases as a most unusual coincidence. Dr. James H. Warren, associated with the author, has done all the laboratory and fluoroscopic work, and much credit is due him.

# THE CLINICAL SIGNIFICANCE OF TOTAL AND DIFFERENTIAL LEUKOCYTE COUNTS, WITH SPECIAL REFERENCE TO ACUTE INFECTIONS.\*

BY WALTER CLINTON JONES, M.D.

DIRECTOR, PATHOLOGICAL DEPARTMENT, ST. VINCENT'S HOSPITAL, BIRMINGHAM,  
ALABAMA,

AND

CLARA ENEERIE BROWN,  
BIRMINGHAM, ALABAMA.

(From the Pathological Department of South Highlands Infirmary, Birmingham, Alabama.)

AFTER a thorough review of the extensive literature on this subject, we have formulated the following brief conclusions as being especially pertinent to the theme in hand.

I. **Total White Count and Percentage of Polymorphonuclears.** (1) The majority of writers agree that in most acute infections the total number of leukocytes in the blood is a measure of the patient's resistance and that the percentage of polymorphonuclears is an index of the severity of the inflammation. To Sondern<sup>1</sup> very largely belongs the credit of establishing these two all important principles. (2) Some authorities rely mostly on the total count, while others depend more on the percentage of polymorphs; but reliance on either to the exclusion of the other is frequently misleading. Of the two, however, the differential count probably has the greater value; but neither should be omitted in any critical case.

II. **Lymphocytes.** (1) Reduction in the number of lymphocytes below normal, especially below the normal number per cubic millimeter, is an unfavorable development; and an increase in their number, if not too excessive, is a favorable prognostic point. This conclusion seems to have been reached especially in tuberculosis, but it most likely applies also to various other diseases both acute and chronic. (2) The significance of an increase or a decrease in the number of small lymphocytes alone or of the large ones exclusively, does not seem to be understood.

\* Read before a joint meeting of the Birmingham Pathological Society and the attending staff of South Highlands Infirmary, February 11, 1921.

<sup>1</sup> The Present Attitude of Blood Examination for Diagnostic Purposes, Boston Med. and Surg. Jour., 1905, 153, 690-692. Idem, The Present Status of Blood Examination in Surgical Diagnosis, Med. Rec., 1905, 67, 452-455. Idem, Value of the Blood Count in Sepsis, New York Med. Jour., 1906, 83, 1245-1246. Idem, The Value of the Differential Leukocyte Count in Gynecology and Abdominal Surgery, Med. Rec., 1906, 70, 989-990. Idem, The Value of the Differential Leukocyte Count in Diagnosis, AM. JOUR. MED. SC., 1906, 132, 889-891.



III. **Indexes of Body Resistance.** Several of these have been originated by various workers in this field. That of Walker's<sup>2</sup> we think is the best. It is computed in the following manner: He takes 10,000 as the highest possible normal total leukocyte count and 70 as the greatest possible normal polymorphonuclear percentage. For each rise of 1 per cent of the polymorphonuclears above 70 there should be an increase in the total count of 1000 above 10,000. Thus if the polymorphonuclear percentage is 80 (10 above 70) the total count should be 20,000 (10,000 above 10,000), in order to make the index normal, or zero. If in this instance the total should rise to 25,000, the index would be +5; if to 30,000, +10, etc. On the other hand, still assuming the polymorphonuclears to be 80 percent, if the total leukocytes were only 15,000 they would be 5000 lower than they should be, making an index of -5; if they were only 10,000 the index would be -10, etc. In the cases of pneumonia, influenza, measles and empyema, which Walker cites, the index nearly always is positive if the disease is progressing favorably; negative, if it is serious; and invariably negative in all fatal cases.

IV. **Miscellaneous Data.** Ether anesthesia, operative trauma, moderate shock, moderate hemorrhage, physical exercise, reclining posture, short cold baths, pregnancy, normal digestion, diurnal factors, geographic location, elevation and personal idiosyncrasies usually cause more or less increase in the total white count.

**Personal Investigations.** This description of our work is in the nature of a report preliminary to further efforts along these lines. Although our conclusions are, we think, in the main correct, yet they are to some extent tentative, because knowledge in this field of hematology is by no means complete at present.

Our counts were made by means of a Levy counting chamber with Neubauer rulings. Two hundred or three hundred cells were enumerated each time. The blood samples were taken at various times of the day; it usually was impracticable to get them the same hour each day when two or more counts were made on the same individual. From one to fifteen counts were made on each patient, at intervals varying from six hours to twenty-four days.

Wright's stain was used, although we were fully aware of the fact that some specialists in this field do not hold it in high esteem. As far as we are concerned, we feel very grateful to Wright for devising his stain, for without rapidity of method thus made possible we would have been unable to obtain sufficient time from our busy routine to make the examinations which form the basis of this article. While Wright's stain does not bring out all cytologic details that every hematologic investigation requires, yet it was

<sup>2</sup> An Index of Body Resistance in Acute Inflammatory Processes, *Jour. Am. Med. Assn.*, 1919, 82, 1453-1457.

ample for our purpose, for we needed a stain which would enable us merely to distinguish polymorphonuclears from lymphocytes and also differentiate these two groups from the various other commoner varieties. Wright's stain when rightly handled accomplishes these results satisfactorily.

Our counts were made on patients suffering from the following diseases: 21 cases of appendicitis ranging in severity from very mild to fatally severe; 2 cases of puerperal infection; 2 secondary infections of laparotomy wounds; 1 each of the following: abscess of the kidney; abscess of retroperitoneal sarcoma; pelvic abscess following radium treatment; abscess of the lung following traumatic infection of the arm; abscess of tooth; acute pelvic gynecologic infection (?); eclampsia; postpneumonic empyema; cyst of spleen; acute lobar pneumonia; infection and gangrene of ovarian cyst complicating pregnancy; chronic salpingitis and retroflexion of uterus; recurrent pyelitis with salpingitis (?); chronic cholecystitis; nephroptosis; incomplete intestinal obstruction; mucous colitis; pyelonephritis; mild cerebral hemorrhage; posttyphoid lumbago; uterine hemorrhage, chronic cervicitis, and retrodisplacement of uterus; myocarditis, endocarditis, and appendicitis (?); one undiagnosed case. All of above patients except 4 were occupants of South Highlands Infirmary.

We will discuss our cases in regard to the hematologic principles we wish to elucidate rather than according to the various kinds of inflammatory diseases we have investigated, for in the class of infections considered in this report we found these principles to be practically the same, regardless of the nature of the invading bacteria or the portion of the body attacked.

**General Explanation of Figures.** The total leukocyte count was obtained according to the usual method. The percentage of polymorphonuclears was ascertained by the ordinary procedure of counting spreads on slides. The total polymorphonuclears per cubic millimeter was computed by multiplying the total count by the percentage of polymorphonuclears. Walker's index was worked out according to the method already described (p. 554). The total number of lymphocytes per cubic millimeter was obtained by multiplying the total leukocytes by the percentage of lymphocytes (taken from the differential count).

The line in the upper portion of each figure extending to the right on a level with "10,000" indicates the highest possible normal number of total leukocytes. The first line below this designates 7000 as the highest possible normal total number of polymorphonuclears. The line on a level with "70" signifies the highest normal percentage of polymorphonuclears. The line to the right from "zero" denotes normal resistance according to Walker's index. The lowest line on the right side indicates 1000 as the lowest possible normal number of lymphocytes per cubic millimeter.

The vertical columns of arabic numerals are arranged so that exactly the same amount of vertical space is allowed for a change of 1000 in the total leukocytes or total polymorphonuclears, for a variation of 1 per cent in the percentage of polymorphonuclears, and for a shifting of one point in Walker's index. The vertical intervals under "Total Lymphocytes" have no definite relations like those just described.

1. **Total Leukocyte Count.** Many if not the majority of clinicians look upon a rise of the total leukocyte count above normal in most acute inflammatory diseases as one of the indications of the presence of infection, and consider that a fall back toward normal means an improvement in the patient's condition; also, that the severity of the process corresponds fairly closely with the degree of the leukocytosis and the range of its fluctuations. The first point to stress in this connection is that the total count often is of little value in estimating the state of the patient. In fact, it may be positively misleading. For example, in Fig. 4, the fall of the total count from November 11 to 19 marks an exacerbation of the patient's infection. In Fig. 2 note that throughout the illness there was relatively little change in the total count and that it fell only from 16,000 to 11,000, a drop not corresponding clinically to the patient's prompt recovery from the operation. In Fig. 6 notice the decline of the total count from June 12 to 17, which parallels a marked aggravation of the patient's condition; the decided rise June 20 to 21 coincides with a very marked clinical improvement. Fig. 5, a fatal case, shows a gradual descent of the total count during the sixteen days immediately preceding the patient's death. This independent behavior of the leukocytic count occurs so frequently that by following along the rises and falls of the leukocytes from count to count one can find in every figure of this paper from one to five instances in which the total number of leukocytes either (1) rises with an improvement in the patient's condition or (2) falls with an exacerbation of the infection or (3) remains practically stationary while the clinical course either improves or gets worse—all three of these combinations being contrary to the significance commonly assigned by clinicians to the total leukocyte count.

On the other hand in many if not most instances the *general trend* of the total leukocytes does go hand-in-hand with the clinical course. Refer to Fig. 1, where the general direction of the leukocytic curve is downward while the patient at the same time makes a good recovery. This parallelism does not hold true, however, if one considers details too closely, for the drops from September 29 to August 1 and from August 3 to 4 were accompanied by aggravations of the patient's infection. But the general direction of the line does point toward the excellent recovery which the patient made. Figs. 2, 3, 4 and 6 illustrate cases precisely similar to the

one just described. Note also in a fatal case, Fig. 5, that the general course is downward, but not as markedly so as in the cases which recovered.

The most outstanding fact to be observed concerning the clinical significance of the total number of leukocytes is that they constitute the chief hematologic manifestation of the amount of resistance the body is making against the invading organisms. It is always a bad sign for the total leukocytes to register low unless the percentage of polymorphonuclears is correspondingly small. If the latter are high and the total leukocytes are low this combination means that a poor resistance is being offered against a severe inflammation—a situation which must be corrected if the patient is to recover. (See Fig. 5, September 24; this patient died. Compare Fig. 2, June 27, and Fig. 6, June 18 and 20.)

2. **Total Polymorphonuclear Count.** This parallels closely the total leukocytes. In comparing the two lines it is seen that they almost invariably lie relatively close together when the patient's condition is more or less serious, and separate from each other with clinical improvement. In Fig. 1, September 29, the patient's resistance is good and the two lines lie well apart; by October 1, the resistance had decreased markedly and the lines are twice as close together. On October 3 there was a decided improvement in the resistance and the lines at once separate from each other. In Fig. 6 note how close these lines lie to each other June 18 when the patient is at her worst, and how they gradually diverge as she recovers. All of the figures accompanying this article illustrate this principle very well. The approach and the spread of these two lines in relation to each other is an entirely new discovery of the senior author, and taken alone, independent of other hematologic findings, it constitutes an excellent guide to the patient's true clinical state.

3. **Percentage of Polymorphonuclears.** Of all the elements of a leukocyte count this probably is the most valuable. If these run high they mean a severe inflammation which usually, but not always, is purulent or gangrenous or both; and if the patient is to recover, relief must be obtained either spontaneously or by artificial means.

We would like to emphasize at this point the futility of trying to foretell with certainty whether pus is present by the degree of polymucleosis. (See Tables 1 and 2, which show that pus was found in the lesions with percentages of polymorphonuclears ranging from 64 to 94, and that pus was absent with percentages of 64 to 93.) But whether there be pus and gangrene or not a high polymorphonuclear count means practically without fail a severe inflammation or a marked toxemia of some kind. The nature of the invading bacteria very likely plays a part in this respect. Thus we know that certain streptococci may produce a

severe inflammation and marked toxemia with but little or no purulent exudate. On the other hand, bacteria of low virulence, like many strains of colon bacilli, may produce large abscesses with so little toxemia that there is no reaction on the part of the blood. Again, the infection may be virulent but the patient fails to put up a fight; in this case the blood is negative. Finally, the infected area may be so thoroughly walled off that there is no absorption of toxins and hence no hematologic response.

From a practical standpoint, however, the problem of diagnosis usually is solved sufficiently to determine an effective mode of procedure by correlating the blood findings with the clinical history and the physical examination. In this connection one must remember that high counts are of greater value than low ones in making a positive diagnosis, unless the latter follow the former. For example, in Fig. 4 a drop in the polymorphonuclears from 88 per cent to 68 per cent from November 29 to December 18 can mean but one thing, namely, a marked improvement in the pathologic process. The successive drops in Fig. 6, June 18 to 25, have exactly the same significance. The opposite sequence of a high following a low percentage has precisely the opposite meaning and can be relied upon implicitly. (Refer to Fig. 5, September 21 and 24, and Fig. 6, June 17 and 18.)

**4. Polymorphonuclear (Walker's) Index of Body Resistance.** The nature of this index and the method of its computation have already been explained. We have been able to verify practically every claim that Walker makes for it. Minor fluctuations, as one might expect, frequently seem to have no clinical significance. However, in practically every case of ours that terminated favorably the index ascended well above normal (zero) and many times very far above it. (See Figs. 1, 2, 4 and 6, where the rises at recovery were only a moderate distance above zero.) In these patients recuperation was satisfactory but not as prompt and complete as in the case illustrated in Fig. 3, where the index rose enormously above normal. The case shown in Fig. 5, which ended fatally, had a very low index, never attaining normal.

Caution should be exercised in interpreting Walker's index when on or near the zero line except in connection with the percentage of polymorphonuclears. While in patients that have practically recovered the index may be at or near normal, the same is also true frequently of those suffering severe inflammations. For example, in Fig. 4, December 18, the index is approximately at zero, the total and polymorphonuclear counts are within normal limits and the patient has overcome almost completely her very severe infection. Now compare Fig. 6, June 12, p.m., when also Walker's index is at zero but the polymorphonuclears are at 88 per cent. The following morning the index has dropped to six below normal, and laparotomy the same day revealed an infected

gangrenous ovarian cyst. Compare again two more cases: in Fig. 1, October 18, the index is near the zero line (slightly above), the total leukocytes and the percentage of polymorphonuclears are practically normal and the patient has almost completed a clinical recovery. Compare Fig. 3, January 17, where the index also is approximately the same but the patient's polynuclears are 82 per cent, and he is very ill, suffering from a severe toxemia. The importance of always evaluating a normal Walker's index in connection with the percentage of polymorphonuclears may be better appreciated by likening a normal index accompanied by a normal polymorphonuclear count to a good dam with normal water-pressure behind it. No questions are asked; no fears arise. On the other hand normal index with a high polymorphonuclear percentage is like the same dam with a high water-pressure back of it. The question is asked at once, will the dam hold the flood? And one may fear the consequences if the structures should break. Similarly, if a patient's index is normal and his polymorphonuclears are high, one seeks to estimate whether the patient will be able to maintain his resistance and what the consequences will be if he fails.

Of course what one dreads most of all are marked depressions in the index caused by a high polymorphonuclear percentage and a low total leukocyte. (See Fig. 1, October 2; Fig. 2, June 27; Fig. 3, January 20; Fig. 5, September 24 and 27; and Fig. 6, June 18 and 20.) If a patient does not recover with reasonable promptness from such low readings as these he is almost sure to suffer dire consequences.

**5. Total Number of Lymphocytes per Cubic Millimeter.** These were computed by multiplying the total leukocyte count by the percentage of lymphocytes. Three features are particularly outstanding in regard to the total lymphocyte count:

Taken by itself it constitutes a very reliable index to the patient's condition. The lymphocytes almost invariably increase with the patient's improvement and decrease when the infection is worse; and they always rise high when recovery has become complete. Every figure in this article illustrates this point. In fatal cases the total lymphocytes remain close to or below lowest normal (1000). (See Fig. 5.)

The second point of interest is the discovery the senior author has made that the total lymphocyte curve parallels almost exactly the polymorphonuclear (Walker's) index of resistance. Every figure shows this feature. Why in rare instances (*c. g.*, Fig. 3, February 1 to 5) they run in opposite direction we are as yet unable to explain.

Concerning the relation of the total lymphocytes to the total leukocytes and to the percentage of polymorphonuclears, practically the same can be said that was stated in connection with the

polymorphonuclear (Walker's) index. The points to be noted are as follows: (a) A low lymphocyte count with a low or only moderately high percentage of polymorphonuclears is not a bad sign; and if at the same time the total leukocytes are high the outlook is favorable. (See Fig. 1, October 3 and 4.) This combination of low lymphocytes and low percentage of polymorphonuclears does not occur often, because when the percentage of polymorphonuclears goes down the number of lymphocytes per cubic millimeter usually (but not always) increases reciprocally. (b) A low total lymphocyte enumeration with a high percentage of polymorphonuclears and a high total leukocyte count indicates a more or less serious condition. This is the most frequent combination found. (Refer to Fig. 4, November 11; and Fig. 6, June 12.) (c) A low total lymphocyte count with a low or only moderately high total leukocyte count and a high percentage of polymorphonuclears constitute a combination which signifies a very serious state that frequently ends fatally. This situation is encountered in a rather small percentage of patients. (See Fig. 4, November 19 to 29, and Fig. 5, September 24) [a fatal case].

6. **Correlation with Clinical Findings.** An extensive blood picture as described above has its final significance only when evaluated in connection with the clinical history and the physical examination. Two features in this connection deserve special emphasis: (a) The fact whether the organ involved is vital and (b) the possibility of relief from the inflammation either spontaneously or by surgical or by other procedures. For example, in Fig. 4, we have a blood picture which betokens a serious state when studied alone; but when one considers also the clinical facts that the abscesses did not invade vital organs and also that they could be and were efficiently treated (by drainage) we find a large part at least of the explanation of the patient's complete and fairly prompt recovery. (Study Fig. 5, too.) Here every feature of the blood picture is bad. The total leukocytes are low, indicating a poor resistance; the percentage of polymorphonuclears is high, demonstrating a severe infection; the index is very low and the total lymphocytes are down. The organ involved, a lung, is a vital one; and efficient treatment (by drainage or otherwise) was very difficult. If the part of the body invaded had been the appendix the patient probably would have recovered, other things being equal; for the appendix not being a vital organ (and being readily accessible) can be removed, and an appendicular abscess can be effectually drained. In Fig. 6, June 18, the blood picture looks very bad *per se*; but when one discovers that it is due to an abscess in the abdominal wall the picture takes on a lighter hue; for the wall of the abdomen is relatively not a vital portion of the body, and it is easy to treat curatively most abscesses which occur in this anatomic location.

7. **The Extent and the Form of the Leukocytic Blood Picture.** When making a blood examination we wish to emphasize the importance in all serious cases of including most if not all of the features described above. Without the total leukocyte count one is in the dark as to the amount of resistance the patient is offering. Without the percentage of polymorphonuclears one does not know the severity of the inflammation. Without Walker's index one is deprived of a lucid means of expressing the relationship between the total leukocytes and the percentage of polynuclears. Without the total lymphocyte estimation one misses valuable confirmatory evidence. A knowledge of the total number of polymorphonuclears per cubic millimeter is a distinct aid but is of the least value of any of the five features constituting our blood picture. The most important of all, without doubt, is the percentage of polymorphonuclears.

An examination of this sort may seem long and complicated to one who has not done several of them; but all that is involved beyond an everyday total and differential count is a few brief calculations and the printing of the blank charts. In our laboratory at present we are making the charts by hand; but later, when we feel we have digested the subject more thoroughly, we will have the printer stock us with a supply.

We wish to direct attention especially to the manner in which the data are charted. It is utterly impossible to convey adequate information to the mind through the eye by means of written characters collated in ordinary tables. We made tables for all of our cases, and of course obtained valuable knowledge from them; but the added information acquired when we transformed these plain tables into graphic charts was like a flood of light thrown into a poorly illuminated room. Charts with horizontal lines, one for each element of the picture (or constructed according to this principal) are very essential. This method gives perspective and throws into the foreground certain important features which otherwise remain unnoticed.

**The Value of a Small Number of Leukocytic Counts.** Very many writers emphasize the importance of making a considerable series of counts on any given patient in order to acquire information of appreciable use, and they deprecate the value of one count alone. We wish to emphasize the value of single counts. For example, in Case 6, Table 1, the surgeon relied completely on the blood picture from one examination to determine immediate operation. In nearly every case charted in this table the high percentage of polymorphonuclears, the negative Walker's index, the relatively small number of lymphocytes and the relatively large total count obtained from single examinations constituted exceedingly valuable evidence, and the story which these findings told was almost invariably confirmed clinically. On the other hand, low percent-



ages of polymorphonuclears and positive indices of resistance helped greatly to confirm the clinical diagnosis of mild and non-purulent lesions. Nearly all of these blood features were confirmed by operation or otherwise.

**Conclusions.** 1. That the details of the total white count considered alone have but little value as a prognostic index is evinced by the fact that segments of the curve may rise or fall or remain stationary while the patient's true condition is becoming either better or worse or is unchanged. However, the *general trend* of a curve composed of several counts, disregarding minor ups and downs, usually does have significance: a general downward course, other things being equal, parallels clinical improvement; an upward direction is of ill omen, and a horizontal course indicates but little change. We wish to emphasize most of all the fact that the total leukocyte count is a measure of the amount of resistance the patient is offering against the inflammatory process.

2. The count of the total polymorphonuclears runs somewhat parallel with that of the total leukocytes. However, this parallelism is not complete. We have made the discovery that these lines approach closest to each other when the patient's condition is the worst, and are farthest apart when he has returned to normal. Thus the convergence and the divergence of these two lines constitute a very good prognostic index to the course of an inflammatory disease.

3. The percentage of polymorphonuclears constitute a very reliable indication of the severity of an inflammation. A high percentage means a severe process almost without fail, and a low figure means a mild infection; but probably the low count cannot be relied upon to demonstrate absence of infection and especially of pus to the extent that a high count can be trusted to indicate a severe infection—usually with pus or gangrene or both.

4. The polymorphonuclear (Walker's) index of resistance is an exceedingly reliable prognostic guide. However, readings near normal (zero) must be interpreted in connection with the other features of the blood picture, especially the percentage of polymorphonuclears. If these are high the condition is serious or at least may become so, while if the polymorphonuclears are within the normal limit there is but little cause for apprehension. A very low index means by itself a serious condition, for the index cannot drop far unless the percentage of polymorphonuclears (measuring the severity of the inflammation) rises high or relatively high and unless at the same time the total leukocytes (indicating body resistance) register low or relatively so.

5. The total number of lymphocytes per cubic millimeter constitutes a very reliable index of a patient's state of resistance. A reading near or especially below lowest normal (1000) is unfavorable. The auspicious cases remain well above this danger

line. We have made the original discovery that the curve of the total lymphocytes parallels Walker's index (in the class of cases investigated), and also it seems to have practically the same significance as Walker's index; but like the latter it must be interpreted in connection with the percentage of polymorphonuclears and the total leukocyte count.

6. A hematologic picture has its true significance only when interpreted in connection with the clinical findings. While many of these are important, we wish to emphasize two: (1) the fact whether the part of the body concerned is vital, and (2) the possibility of relief, either spontaneously or by surgical or other means.

7. We consider that none of the features of the hematologic picture we have presented should be omitted in examining serious cases. However, if one must choose, there is no reasonable doubt that the total number of polymorphonuclears per cubic millimeter is the least important element and that the *percentage* of these same cells is the most important.

8. We desire to emphasize the value of a single blood examination, although, of course, we always prefer to get two or more counts, if possible, on any given case.

9. Negative findings have much value but are not to be relied upon as implicitly as positive ones.

10. We wish to emphasize the importance of depicting blood pictures in the form of graphic charts as described in this article, and we maintain that tables with written characters only, which omit the all expressive systems of lines, are very inadequate.

We regret that space will not permit the publication of our bibliography of about two hundred references.

TABLE I. This is made up to show the *value* of *single counts* in cases in which more than one enumeration was made. From two to twelve counts were made on each of these patients. One count from each case, in nearly every instance the one immediately preceding operation, was selected for this table. In Case 8 there was no visible discharge except the menstrual flow. The exact nature of the lesion never was ascertained because the patient did not come to operation. The count in Case 1 was immediately postoperative, which almost always is higher than a preoperative one. In case 47 the count was taken four days after operation—after the patient had improved greatly.

This table illustrates, among other features, the futility of attempting to diagnose with certainty the presence of pus by the percentage of polymorphonuclears or by the total count. Pus was present in percentages ranging from 64 to 94, and in total counts from 7,200 to 28,300. Pus was absent in percentages varying from 64 to 93, and in totals from 8,000 to 28,400. These findings are explained by the fact that there may be but little pus in a virulent infection and much pus in a mild one,

TABLE I.

Case.	Per cent polymorphonuclears.		Total leukocytes		Diagnosis, etc
	Pus or gangrene	No pus	Pus or gangrene	No pus.	
38	77	..	6,500		Abscess of kidney.
14	81	..	14,200		Infection, puerperal; no operation.
21	..	75		11,500	Appendicitis, acute; burn of foot.
8	..	93 (?)		23,500	Infection, acute pelvic; acute gastritis; no operation.
4	81	..	16,000		Abscess of retroperitoneal sarcoma.
1	..	84		28,400	Eclampsia; Cesarean section.
3	..	66		8,900	Appendicitis, acute catarrhal.
2	85	..	28,300		Appendicitis, acute, purulent, gangrenous.
16	86	.	15,400		Appendicitis, acute, purulent, gangrenous.
46	82		22,000		Appendicitis, acute purulent.
47	69	.	12,000		Empyema, postpneumonic. Patient two years old.
32	70	..	7,200		Thrombophlebitis, puerperal, pelvic.
13	.	93		28,200	Cyst of spleen; no gross signs of infection.
	84	.	15,000		Infection, secondary, of laparotomy wound.
7	90		25,000		Pneumonia, acute lobar; no operation.
31	91	.	13,000		Abscess, pelvic; following radium treatment uterus; three operations.
11	89	.	10,000		Abscess of lung; following traumatic infection of arm.
24	91		17,200		Appendicitis, acute, purulent, gangrenous.
5	64		7,400		Appendicitis, acute purulent.
17	..	64		8,000	Appendicitis, subacute.
	87	.	27,000		Infection and gangrene, acute, of ovarian cyst (twisted pedicle).
48	94	..	16,000		Infection, secondary; laparotomy wound.

## BURN OF FOOT—ACUTE NON-PURULENT APPENDICITIS

FIG. 1.—Case 21. Burn on the foot; acute appendicitis. Patient of Dr. S. L. Ledbetter, Jr. Mr. W. O. M. Age twenty-eight years. In hospital, September 25 to October 18, 1920. Patient entered hospital with a burn on the foot. After several days pain in chest developed accompanied by nausea and vomiting. There was no particular tenderness in the abdomen at first. Later, there appeared distinct localizing symptoms in the region of the appendix.

*Operation and Pathology.* Laparotomy by Dr. Ledbetter, October 5, 1920. No drainage. Appendix was large, red and swollen, but there was no macroscopic pus.

*Postoperative Course.* This was practically uneventful. Patient felt bad October 1; better on October 2; better on the 3d; about the same, on the 4th; not so well on the 5th. Temperature and pulse remained practically normal throughout convalescence. He was up in a chair October 13, and went home on the 18th.

TABLE II.

Case.	Total leukocytes.		Per cent polys.		Walker's index.		Total lymphocytes.		Diagnosis, etc.
	Pus or gangrene.	No pus.	Pus or gangrene.	No pus.	Pus or gangrene.	No pus.	Pus or gangrene.	No pus.	
6	18,800	.....	95.5	.....	-16.7	.....	660	3,900	Appendicitis, acute; no macroscopic pus; gangrenous mucosa.
9	.....	12,200	.....	64	.....	+8.2	.....	1,930	Appendicitis, chronic; ulcer, gastric.
10	.....	8,200	.....	71	.....	-2.8	.....	2,730	Appendicitis, chronic.
12	.....	9,100	.....	66	.....	+3.1	.....	1,260	Salpingitis, chronic; retroflexion of uterus.
15	.....	6,000	.....	65	.....	+1.0	.....	.....	Pylitis, recurrent; salpingitis (?); no operation.
18	11,000	.....	84.0	.....	-12.4	.....	1,220	.....	Appendicitis, acute; pus abundant.
19	8,000	.....	50.5	.....	+11.5	.....	3,120	.....	Appendicitis, acute; amount of pus very small.
20	.....	6,800	.....	59	.....	+7.8	.....	2,210	Appendicitis, chronic; cystic ovary.
22	.....	9,500	.....	57	.....	+12.5	.....	3,090	Appendicitis, chronic.
23	14,300	.....	92.5	.....	-18.2	.....	715	.....	Cholecystitis, subacute; pus (?)
25	24,900	.....	83.5	.....	+1.4	.....	3,490	.....	Appendicitis, acute; gangrene; abundant pus.
27	.....	13,600	.....	85	.....	-11.4	.....	1,630	Nephroptosis; no operation; pus (?)
28	15,300	.....	87.5	.....	-12.2	.....	1,610	.....	Appendicitis, acute; large amount of pus.
29	30,100	.....	95.0	.....	-4.9	.....	1,050	.....	Appendicitis, acute; gangrene; much pus.
30	27,300	.....	92.5	.....	-5.2	.....	1,230	.....	Appendicitis, acute; gangrene; much pus.
33	.....	8,300	.....	56	.....	+12.3	.....	3,200	Undiagnosed; no symptoms of acute infection; no operation.
34	.....	6,000	.....	70	.....	+4.0	.....	1,560	Obstruction of intestine, incomplete; no operation.
35	10,400	.....	65.0	.....	+5.4	.....	3,220	.....	Abscess of teeth, chronic; very little pus; teeth extracted.
36	.....	6,200	.....	57	.....	+9.2	.....	2,390	Appendicitis, chronic.
37	24,400	.....	85.0	.....	-0.6	.....	2,810	.....	Appendicitis, acute; gangrene; much pus.
39	.....	10,200	.....	70	.....	+0.2	.....	2,350	Colitis, mucous; no operation.
40	.....	6,200	.....	65	.....	+1.2	.....	1,740	Pylonephritis; symptoms not acute; no operation.
41	.....	10,300	.....	60	.....	+10.3	.....	3,910	Hemorrhage, mild cerebral; no operation.
43	.....	15,200	.....	74	.....	+1.2	.....	2,900	Myocarditis and endocarditis, subacute; appendicitis (?); no operation.
44	.....	8,000	.....	65	.....	+3.0	.....	2,560	Lumbago, posttyphoid; no operation.
45	.....	10,400	.....	63	.....	+7.4	.....	3,330	Hemorrhage, uterine; cervicitis, chronic; retrodisplacement of uterus.
Average	18,500	9,100	83.7	65.4	-5.2	+5.1	1,910	2,540	
Range	8,000 to 30,000	6,200 to 15,200	56.5 to 95.5	57 to 85	-18.2 to -11.5	-11.4 to -12.5	660 to 3,490	1,260 to 3,910	

TABLE II.—This is made up from patients on whom *single counts only* were taken. All were operated upon unless otherwise stated. Under total leukocytes note that while the average count is much higher in the purulent than in the non-purulent cases, yet it is possible to have pus with rather low counts, for example, 8,000 and 10,000 (Cases 19 and 35). In these instances, however, the amount of pus was so small as to be almost negligible. When any considerable amount develops the counts run from 12,000

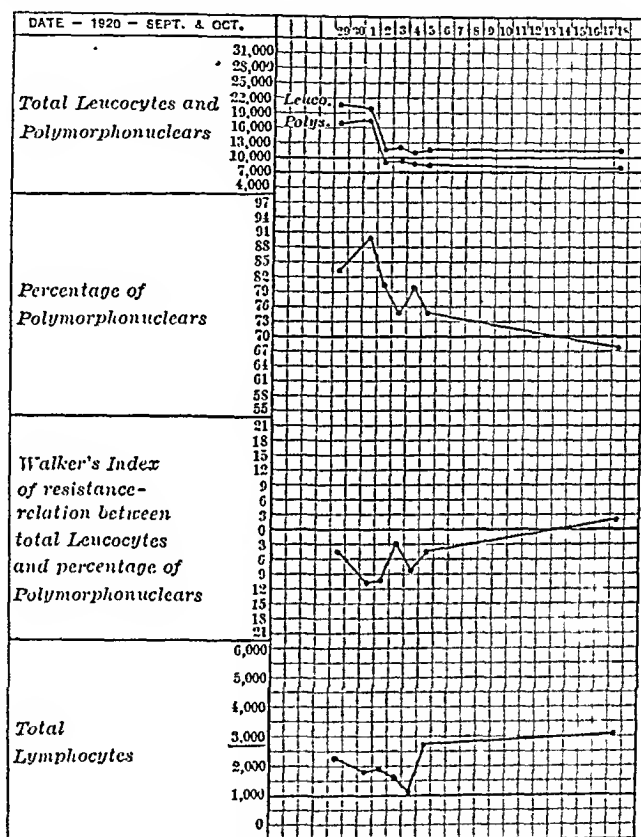


FIG. 1.—See general explanation, p. 555, and description in text.

to 30,000. And still with a high count there may be little or no pus (Case 6). In the non-purulent cases none of the counts are high, the largest being 15,200 (Case 43). Note that the range is 100 per cent greater with the purulent lesions.

In regard to the percentage of polymorphonuclears a low figure does not exclude pus, but the amount is apt to be small, for example, 56.5 per cent and 65 per cent in Cases 19 and 35. Percentages ranging from just above 80 to 95 show marked virulence and at the same time considerable pus usually, but not always; for,

observe that Case 6 with a percentage of 95.5 exhibited no macroscopic pus. The range of variation is greater by 30 per cent in the purulent than in the non-purulent cases.

Walker's index is usually minus in the pus cases and plus in the clean or relatively clean ones. Notice that the pus column has only three plus indices, two of which scarcely belong here because of the very small amount of purulent exudate. In the no-pus series there are only two minus indices. The purulent cases average minus 5.2 and the non-purulent ones plus 5.1.

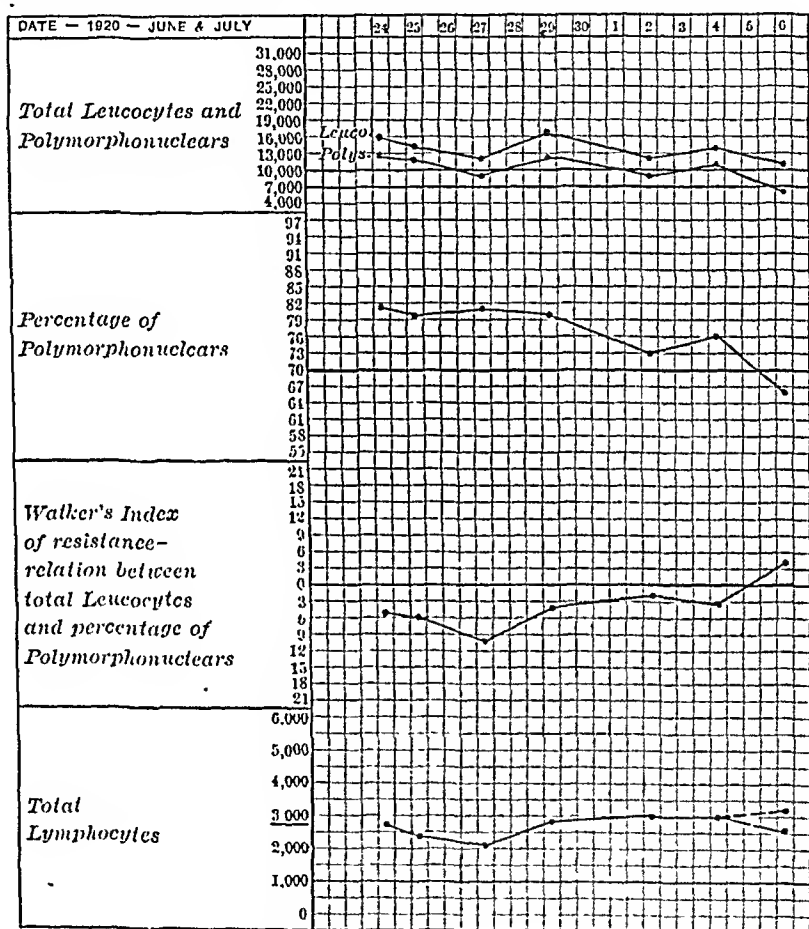


FIG. 2.—The count July 6 showed an erratic rise of the endothelial leukocytes to 8 per cent; this increase occurred at the expense of the lymphocytes. By counting the excess of endothelial in with the lymphocytes a slight increase in the total lymphocytes is produced as indicated by the dotted line. For further elucidation, see general explanation, p. 555, and description in text.

The total lymphocytes average lower by about 30 per cent in the purulent than in the non-purulent conditions. Also the range is somewhat greater in the former than in the latter. And still more significant are the low levels, well below 1000, to which the purulent cases now and then drop (Cases 6 and 23). This almost never occurs with the non-purulent lesions.

FIG. 2.—Case 4. Abscess of retroperitoneal sarcoma. Patient of Drs. E. M. Prince and D. S. Moore. Mrs. S. J. A. Aged forty-five years. In hospital June 24 to July 8, 1920. She had been in the hospital for a few days prior to the middle of June, 1920, with a history of gall-stone colic, and a diagnosis of cholelithiasis was made at that time. No other symptoms were present, and she was discharged without operation.

She returned June 24, 1920, suffering with acute pain, which had begun five days previously and which extended over her entire abdomen. Preoperative diagnosis of appendicular abscess was made.

*Operation and Pathology.* Laparotomy by Dr. E. M. Prince, June 24, 1920. Drainage. A large retroperitoneal sarcoma was found, in the interior of which was a large abscess. One large gall-stone was found in the gall-bladder.

*Postoperative Course.* On the whole she made a rather uneventful recovery. Temperature, June 24 to 28 was 97° to 102°; 29 to 30, 98° to 100.4°; July 1 to 3, 99° to 101°; 4 to 8, 98° to 100°. There were marked rises and falls the same day during the early part of her illness. Patient's pulse followed her temperature, ranging from 80 to 120. It was weak a few hours after operation, when hypodermoclysis was given. Respirations varied from 20 to 30. She suffered much from gas pains, etc. Many enemas were given and she was catheterized several times. Her condition was the least favorable on June 27. The wound drained freely and her condition improved until she sat up with a back-rest July 7, and was taken home the following day in good condition.

FIG. 3.—Case 46. Acute purulent appendicitis. Patient of Drs. E. M. Prince and D. S. Moore. Mr. R. S. Aged twenty-seven years. In hospital January 17 to February 6, 1920. His symptoms were pain in the epigastrium, nausea and vomiting; moderate temperature; tenderness and rigidity in the region of the appendix. Trouble began the forenoon of the day the patient entered the hospital, and he was operated the same day about 8.00 P.M.

*Operation and Pathology.* Laparotomy by Dr. Prince, January 17, 1921. Drainage. Appendix was ruptured and there was a moderate amount of pus. No adhesions had formed.

*Postoperative Course.* Recovery was very satisfactory. Wound drained freely and there was still a little discharge when the patient left the hospital. Temperature at the time of operation was 102.68; this had fallen to normal by the nineteenth, and there was no subsequent rise. Pulse corresponded to temperature. He was on a back-rest the third and walked the sixth.

FIG. 4.—Case 31. Pelvic abscess; secondary in right iliac region; tertiary in left iliocostal space. Patient of Drs. E. M. Prince and D. S. Moore. Mrs. W. H. Aged forty years. In

hospital November 10, 1920, to January 16, 1921. Patient had received two treatments of radium for uterine hemorrhage, the last exposure being made a few days prior to her entrance to the hospital. After her first treatment her bleeding was lessened and after the second it stopped altogether; but a dark, malodorous vaginal discharge of moderate quantity appeared. During the twenty-four hours before she came into the hospital she had three chills and her temperature rose as high as 104°. She was observed for ten days in the hospital, when finally induration in addition to tenderness developed in the hypogastrium.

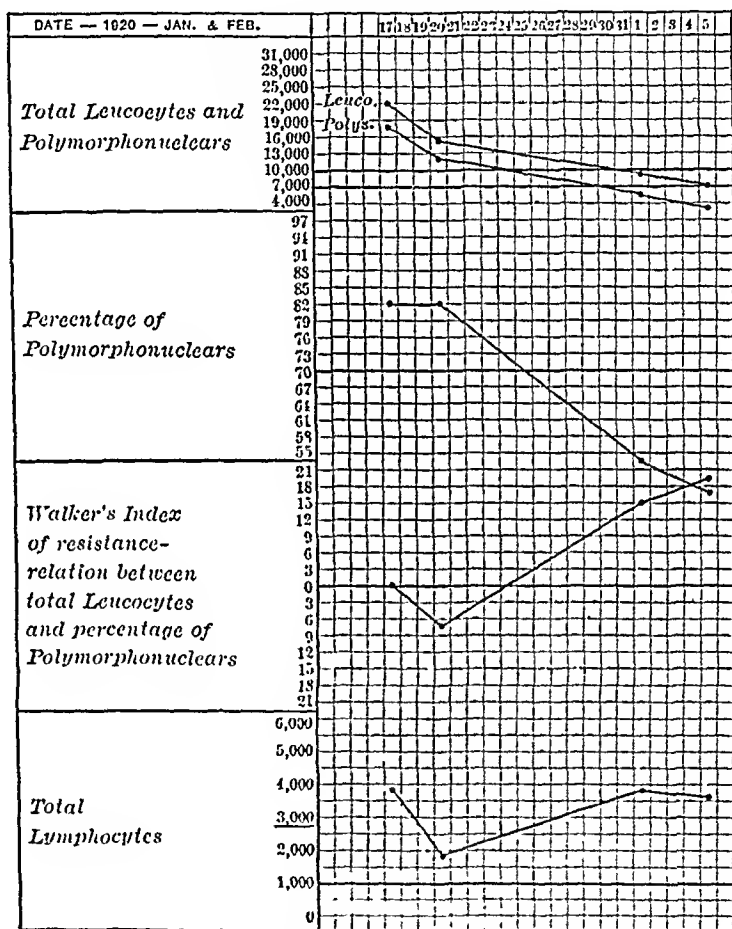


FIG. 3.—See general explanation, p. 555, and description in text.

*Operations and Pathology.* Laparotomy by Dr. D. S. Moore, November 20, 1920. Median incision above symphysis pubis. Drainage. A large amount of yellow, foul-smelling pus was evacuated; its origin was not ascertained.

November 27. Drainage incision in right inguinal region by Dr. Moore. A considerable, thick, rather malodorous pus was obtained; its source was not ascertained.



December 5. Drainage incision in left iliocostal space by Dr. E. M. Prince. A large amount of thick greenish-yellow pus escaped; its ultimate source was not discovered.

*Postoperative Course.* After the first operation the temperature ranged mostly from 100° to 103°; pulse, 85 to 105; respirations, about 20. After the second operation there was but little apparent change. Following the third incision the temperature, pulse,

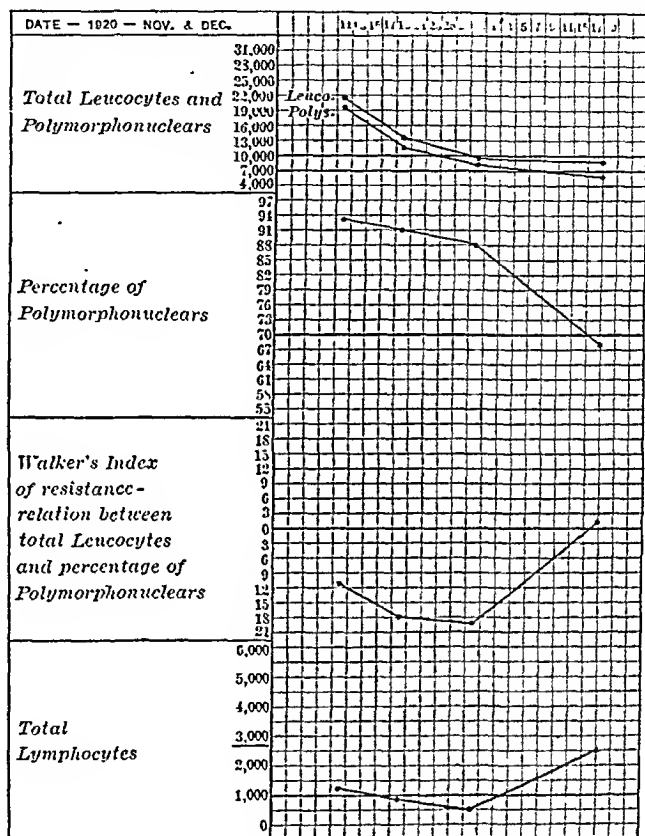


FIG. 4.—See general explanation, p. 555, and description in text.

etc., gradually returned to normal, reaching it for the first time permanently about December 30, although by December 18, there was marked improvement. All drainage had ceased by January 14, 1921, and January 16 the patient was discharged cured.

#### TRAUMATIC INFECTION IN RIGHT ARM; METASTATIC ABSCESES IN LUNGS.

FIG. 5.—Case 11. Traumatic infection in right arm; metastatic abscesses in lungs. Patient of Drs. E. M. Prince, D. S. Moore

and C. Lull. Mr. W. J. J. Aged thirty-two years. In hospital September 10 to 28, 1920. Discharged from army on account of beginning locomotor ataxia. About six weeks prior to entering hospital he acquired a traumatic infection of the soft parts of the right arm near the elbow. About the time he entered the hospital signs of a metastatic abscess in the upper lobe of the right lung began to be evident. On September 22, roentgen-ray plates confirmed this diagnosis and showed also an abscess in the left lower lobe.

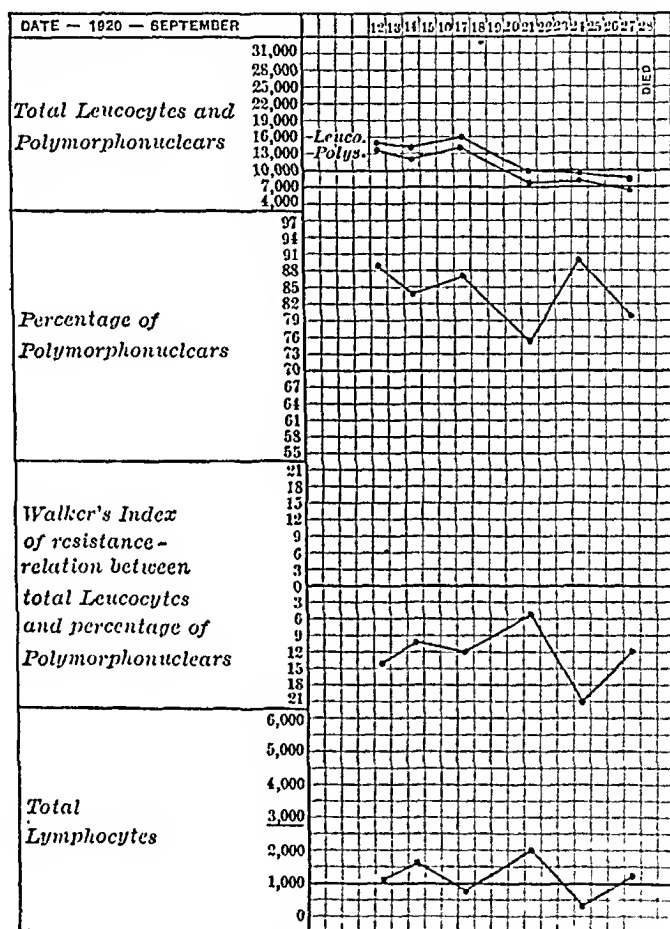


FIG. 5.—See general explanation, p. 555, and description in text.

*Operation and Pathology.* Incision and drainage of abscess in right lung by Dr. D. S. Moore, November 23, 1920. A large amount of pus was found.

*Postoperative Course.* Temperature rose and fell almost daily from about 99° to 104° throughout his illness while in the hospital. Pulse varied with the temperature, ranging from 110 to 140. Respirations were mostly from 20 to 25. There was no improvement after the drainage operation, November 23. He was expected to die November 24, but did not expire until November 28.

FIG. 6.—Case 48. Pregnancy complicated by infected, gangrenous ovarian cyst. Patient of Dr. Edward O'Connell. Mrs. A. McD. Aged twenty-nine years. In St. Vincent's hospital June 12 to 27, 1920. Married nine months. Prior to marriage, menstruation was irregular. Has had no abortions. Patient is about five months pregnant.

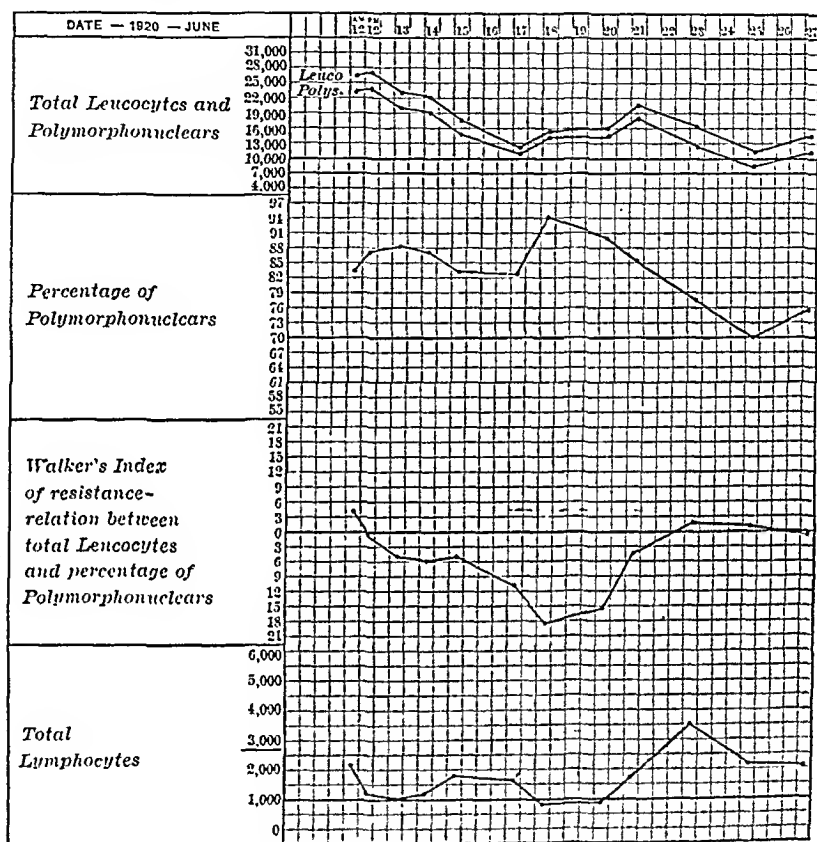


FIG. 6.—See general explanation, p. 555, and description in text.

About three months ago she began to complain of severe pain in the left side of the abdomen at intervals of about four days; this pain lasted four or five hours in each attack. Pulse and temperature were normal during intervals between attacks. She has been constipated and has suffered from headaches for about two months.

*Operation and Pathology.* Laparotomy by Dr. Watkins, January 13, 1921. Drainage. An ovarian cyst, about 18 cm. in diameter, was found, lying on the left side of the lower abdomen. The side of the cyst against the abdominal wall showed signs of moderate

inflammation. The pedicle was twisted and there was considerable beginning gangrene on the side toward the median line.

*Postoperative Course.* Temperature ranged from 96.2° to 100°, reaching the latter figure only once, namely, the day after operation. Pulse before operation was 108 to 110; the rest of the time it ranged from 78 to above 90, reaching 100 only January 19 and 20. Quality was practically normal all of the time. Respirations were 18 to 22, except during the two days before and three days after operation, when they ranged from 22 to 28.

There was some purulent discharge from the wound, especially January 18 to 20; on this latter day a large abscess was evacuated through the drainage opening. General condition of the patient was very good throughout the entire course of her trouble, and she went home January 27 in excellent condition. The pregnancy was not interrupted.

## THE SURGERY OF THORACIC TUMORS.\*

BY ABRAHAM O. WILENSKY, M.D.

NEW YORK.

(From the Mount Sinai Hospital, New York.)

INTRATHORACIC surgery is still a pioneer field. We are fortunate in that much of the necessary groundwork has already been done in the physiologic aspects of the problems of intrathoracic surgery. The recent military emergency was a most valuable experience in that it gave to a large number of men a sense of security in operating within the thorax. So that many men have learned (1) the methods of incision which give maximum visibility within the thorax; (2) that the thoracic viscera may be manipulated without undue shock and without serious disturbance to the patient; (3) to control hemorrhage from the viscera; (4) that the lung may be cut and sutured and that parts of it may be removed safely; and (5) that intratracheal, intralaryngeal or other forms of differential pressure anesthesia are not essential, although they are helpful and advisable when operating within the thorax. All of this experience is of the utmost value for the surgical problems of civil life.

More than anywhere else in the body the successful surgery of thoracic tumors has imperative need for early diagnosis. Then the lesion will be exposed when it is in its simplest and most uncomplicated state; when it is as small as possible, when its removal is not hampered by adhesions to vital structures or made impossible

\* Read at a Symposium on Thoracic Tumors before the Yorkville Medical Society October 17, 1921.

or futile by reason of neighboring or distant metastases; and when the removal of the growth is not made dangerous by reason of secondary infection. Clinicians must constantly keep in mind that many of the so-called inflammatory lung conditions arising in middle or late life are, primarily, tumors and that the symptoms are called forth by superadded infection. I have no doubt that many of these are never discovered and go unrecognized with such generic diagnosis as pneumonia, bronchitis, bronchiectasis or pleural effusion of simple or tuberculous origin. It is of great importance in every case to make use of every available aid in diagnosis. Medical men must learn to submit their patients to the surgeon at an early period of the disease and all men, medical and surgical, must recognize the increasing necessity for exploratory intrathoracic operations if the maximum amount of good is to be ultimately obtained. Thoracotomy for this purpose is a comparatively harmless procedure when done under proper conditions and with proper precautions. Many cases are now seen much too late for the possibility of doing anything of a radical nature because medical men have hitherto been too timid about referring patients with obscure intrathoracic conditions for surgical exploration. It needs to be emphasized again and again how important it is for the medical men, and especially for the general practitioner, to learn the lesson that, when obscure intrathoracic conditions do not clear up fairly promptly under conservative forms of treatment, the chest be opened and adequately explored; under such conditions a wider margin of operability will gradually be obtained and, surely, many more lives be spared for an increasing number of useful years. Certainly unless this helpful attitude is exhibited by the medical men progress will never be made.

The use of the intratracheal and intrapharyngeal forms of anesthesia has been a great stimulus to the development of intrathoracic surgery. The method is especially useful and must be employed whenever there is expectation that both pleural cavities will be opened during the operative manipulations. There is danger of the latter happening as an accident in certain localities even when one is apparently operating in one pleural cavity only. Ordinarily, however, in operations in which only one pleural cavity is opened, the method is not essential and operations can be done with the ordinary forms of anesthesia. Nevertheless the use of the new methods is, decidedly, both a convenience and an advantage and, with their use, the patients do not appear to show to such a large extent the effects of shock or of an acute pneumothorax. When skilfully administered the movements of the lobes of the lungs during respiration are quiet and not excessive and the operator is not hampered in his manipulations. The method has an additional usefulness at the close of the operation when the wound in the chest

wall is to be sutured; the lungs are distended so that they entirely fill the chest and lie in close approximation to their corresponding parietal pleural surfaces, the object being to obviate any dead space, *i. e.*, any pneumothorax, within the pleural cavity.

Access to the interior of the chest can be obtained in a number of ways. In general these conform themselves to one of three types: (1) In the first, an opening is made, as in the usual thoracotomy, by resecting one of the ribs; with this incision visibility is bad and manipulations are difficult. (2) In the second a trap-door is cut in the chest wall by division of the ribs and soft parts; when this is turned out, one side of the flap acting as a hinge, a fairly large opening can be obtained. Visibility is, however, only fair through such a window and access to the organs is only moderately fair except in certain favorable locations. (3) In the third, a long intercostal incision is made in the sixth or seventh interspace and the ribs are forcibly separated by a powerful retractor; additional room is obtained by dividing one or more ribs at the posterior extremity of the incision near their angles. This is the best universal incision; it gives the maximum visibility and access to all the organs within the chest; and manipulations are most easy to execute. When sutured no deformity is apparent. For work on the lungs and diaphragm, or for intrathoracic esophageal operations the incision is not surpassed by any other for access and exposure. The degree of shock seen after operations done through such an incision is at a minimum.

The immediate dangers of intrathoracic operations include the following:

1. **Acute Pneumothorax.** This complication is entirely preventable by the use of the intratracheal, intrapharyngeal or differential pressure forms of anesthesia. In operations involving only one pleural cavity and done without this latter aid the acute pneumothorax is only exceptionally provocative of sufficient embarrassment to excite concern. One usually sees a moderate increase in the number of respirations; more or less cyanosis; and some irregularity of the cardiac action. The embarrassment is only shortlived and very quickly the effects of the pneumothorax are so negligible as to be hardly distinguishable in the clinical picture. In exceptional cases pneumothorax is accompanied with marked disturbances of respiration and circulation which rapidly lead to collapse of the patient and frequently to a fatal termination. I repeat for emphasis that in operations involving both pleural cavities such severe and dangerous forms of acute pneumothorax are only prevented by the use of the new forms of anesthesia.

2. **Mediastinal Flutter.** In normal respiration the integrity of position and action of the central mediastinal portion of the intrathoracic contents is maintained by similar normal conditions in

the adjacent lateral cavities of the chest. If the static conditions on one side are suddenly disturbed by an operatively produced open pneumothorax the entire mediastinal structure is caused to assume a lateral motion because of the passage of air into and out from the open chest wound unless provision has previously existed, or has been introduced during the operation, which is capable of preventing this lateral mobility and of holding the mediastinum immobile in a relatively normal position. This is a very serious phenomenon: It can quickly disturb the normal functions of the heart and of the large vessels and cause marked embarrassment of the pulmonary and general circulation sufficient to bring the patient into a state of collapse from which recovery is rarely possible. The important lesson to be remembered in operating within the thorax, especially upon the lungs, is that the mediastinum be steadied by traction upon the root of the lung, or upon the stumps of the lobes after lobectomy.

The combination of an acute pneumothorax with mediastinal flutter is perhaps accountable for the most severe of these clinical pictures.

3. **Hemorrhage and Shock.** With ordinary care hemorrhage, both intrapulmonary and intrapleural, should be entirely preventable. Shock is an important factor and is aided and abetted by acute pneumothorax or mediastinal flutter, or by both of the latter together.

4. **Opening of the Pericardium when Operating on the Left Side is a Serious Complication.**

The late dangers of intrathoracic operations include the following:

1. *Pleurisy.* Pleuritic effusions commonly appear after operation. This does not seem to be preventable at present and is frequently of a purely mechanical origin. When uninfected they are not dangerous; and when they do not disappear spontaneously they can be withdrawn.

2. *Pneumonia.* Pneumonias are common even when the center of operation is outside of the lung proper. One distinguishes two varieties, the least common of which is the lobar type; much more frequently forms of broncho- and lobular pneumonia are present. All of these are cause for anxiety until they are thoroughly resolved.

3. *Infarction of the Lung Occurs after Lobectomy.* This seems to have important relations to the number and size of the vessels which must necessarily be tied during the operation. Pneumonic infiltrations are naturally common on the borders of the infarctive areas. It is important to differentiate these lesions from intrapulmonary hemorrhages produced during the operative manipulations.

4. *The Great Danger of Operating Within the Thorax Lies in Infection.* Most of the late fatalities occur because of this cause. Infection may take place as a fulminating process, resulting rapidly in death, or, more commonly, more slowly. Infection may take place in the pleural cavity or within the mediastinal cellular tissue. Usually the infection takes the form of an empyema; these can be severe and can result fatally, or they can be mild affairs which serve simply to prolong the healing and the convalescence. A very severe form is due to an anaërobic infection which arises in tumors that are breaking down, and which causes a gangrenous form of inflammation of the entire operative wound. The bad infections are those which take root in the mediastinal cellular tissue; practically invariably these result fatally. These infections are to be feared and guarded against in any operation in which the mediastinum must be opened; in esophageal operations it is the commonest cause of failure. The process has no distinctive clinical signs and is assumed to be present whenever the signs of sepsis appear after any operation in which the mediastinal cellular tissue is exposed. There is no satisfactory method of drainage which can prevent the spread of the infection and death usually ensues with the clinical picture of a high grade of sepsis.

5. Persistent sinuses are fairly frequent after operations on the lungs and are most principally due to bronchial fistulæ. Fistulæ almost always appear after lobectomy but, luckily, most of these close spontaneously.

The question of *drainage* after intrathoracic operations is most important. As a general rule it is to be avoided as much as possible. Its omission is conducive to more comfort in the postoperative period and it permits a better static condition within the thorax for the carrying on of the functions of circulation and respiration. Unfortunately, however, there are many contingencies which demand the insertion of drainage and in such eventualities the drainage should be provided with these purposes in view.

The operability of thoracic tumors and the risks entailed in operation are determined upon general and local grounds; the latter hold similarities to those of tumors in other regions of the body. I shall discuss them with the individual varieties of tumors encountered. Because operations within the thorax are necessarily extensive and productive of much shock, it is necessary to choose one's patients carefully; old decrepit patients or those with advanced circulatory or pulmonary disease are not fit subjects for intrathoracic operations. Even in those who are robust one must be prepared on occasion to fortify the dangerous intervals by the use of transfusions of blood. The total surgical experience in regard to these aspects of intrathoracic surgery is still rather limited by the comparatively small number of cases on record; with more extensive experience our knowledge in regard to these matters must be considerably broadened.



**Chest-wall Tumors.** In actual practice about 72 per cent of chest wall tumors are malignant (carcinoma, sarcoma and hypernephroma); about 20 per cent are benign and of these the common types are fibroma and chondroma; 2 per cent are exostoses or are due to syphilis. About 28 per cent begin in the ribs and about 21 per cent in the sternum. An important group belong to the carcinomata of the breast which spread into the chest wall. Eighty-five per cent of the tumors are found from the second to the seventh decades of life. The influence of trauma seems more marked with these than with tumors arising in other regions of the body. The differential diagnosis must be made between tumor, cold abscess, syphilis, exostosis, aneurysm or dermoid cyst.

With tumors of such accessibility it would seem that the roentgen rays or radium would be very efficient therapeutic agents, but unfortunately this is not so in actual practice, and although isolated cases have been reported by Turner and others, as a general rule these agents are of not sufficient permanent benefit to warrant giving them the place of first choice. Surgery still holds first place and is still the best therapeutic means. A radical operation is possible in about 20 per cent, a palliative excision is permissible in another 25 per cent and the remaining 50 per cent of the cases are hopelessly inoperable. The main contraindications to radical operation are the presence of metastases, or the size of the growth and the extent of involvement of neighboring and contiguous structures. In considering the presence of metastases it is important to remember that not all shadows which are visible roentgenologically in the chest cavity are tumors; and, secondly, in excluding metastatic foci in the bones the Bence-Jones test is very valuable.

The operative technic is not exceptionally difficult. A block excision of the tumor-bearing portion of the chest wall is done by division of the ribs and soft parts; the extirpation naturally requires a sudden acute pneumothorax and collapse of the lung. In the lower ribs the diaphragm must be cut into so that frequently there results a combined thoracotomy. Intratracheal or intrapharyngeal anesthesia is especially useful in chest-wall tumor extirpations. At the conclusion of the operation it is of great importance to be able to distend the lung completely and suture it to the margins of the resultant chest-wall opening. The latter is closed by a plastic of the adjoining skin and soft parts. In certain locations—the anterior thoracic wall—the opposite breast can be mobilized and displaced across to the operated side to obturate the opening; this technic is especially useful with carcinoma of the breast involving the chest wall. When no other technic is available the opening is plugged with gauze. Operations done in more than one stage may be helpful.

The mortality of operation is about 13 per cent. The chief

causes of death are shock (33 per cent), pneumonia (25 per cent) and empyema (25 per cent). Chest-wall tumors show a great predisposition to postoperative infections.

The amount of resultant deformity varies, depending on the number of ribs and the area of chest wall which is resected; but even following wide excisions there seem to be no untoward effects from the absence of ribs and soft parts. In several patients about whom I know, there has been no disability as far as their daily work is concerned.

Recurrences are fairly frequent and multiple operations have been done when the tumors have recurred locally. Early radical extirpation offers the best prospect of cure; even in the presence of extensive involvement it offers the best prospect for a relatively long period of freedom from recurrence.

**Pleural Tumors.** The best classification of pleural tumors is that of Guyot and Parcellier and includes: (1) The benign tumors, including the usually found lipomas, chondromas and fibromas; (2) mixed tumors, such as chondrosarcomas, myxofibrosarcoma and myxoliposarcoma (Pallasse and Roubier); (3) the malignant tumors. Primary malignant tumors of the pleura are among the uncommon neoplasms and are limited to sarcoma (about 20 per cent) and endothelioma (about 80 per cent). There is a good deal of discussion in the literature in regard to the origin of the latter group of tumors; the controversy ranges between those who believe that these tumors originate in the lining cells of the pleura (Ribbert, etc.) and those who believe that they originate in the pleural lymphatics (Schultz and Eppinger).

Up to 1909 there were about 96 cases in the literature. Pleural tumors are found twice as frequently in men as in women and the greatest number are found in patients between forty and sixty years of age. It appears to be a little more common on the right side than on the left.

Pleural tumors are usually insidious in their origin and growth and patients appear for medical care at comparatively late periods when asthenia and cachexia are marked. A frequent picture under which the tumors masquerade is that of a pleural effusion. The differential diagnosis must be made from tuberculosis and tumor of the lung and bronchi. The roentgen ray is usually of little help; it should be done both before and after the fluid is withdrawn. Air or oxygen inflation may demonstrate a tumor which otherwise would be invisible. When effusions are present they may possess characteristic gross appearances; when not, positive information may in many instances be secured from a histological examination of the cellular content of the effusion after the sediment has been appropriately hardened and sectioned (Widal and Ravaut, Warthin, Warren, Mandlebaum).

As regards the therapeutic possibilities, pleural tumors are best

classified with tumors of the chest wall; surgery still holds first place. Guyot and Parcellier found an apparent operability in only 27 per cent of 29 cases. An exploratory thoracotomy is always justifiable in the hope that the anatomic conditions may permit a radical removal.

The late results are very bad; recurrences in the operated cases have always appeared. It is to be hoped that in the future much better results will follow the combined use of operation and radium or roentgen-ray therapy.

**Lung Tumors.** Malignant disease of the lungs forms about 2 per cent of all cancer cases. Statistics tend to show that its frequency is apparently on the increase, but the latter is undoubtedly due to the fact that its recognition is becoming more general among competent medical men. The secondary tumors are more common. Practically all the ordinary varieties of malignant tumor are found to metastasize in the chest—sarcoma, carcinoma, melanoma, hypernephroma, chorionepithelioma, lymphosarcoma and endothelioma. The differentiation is made upon two essential facts: (1) The general and local signs of a lesion in the chest either in the lung or pleura; and (2) the history or demonstration of a primary growth. Chorionepithelioma is known to be able to disappear spontaneously; otherwise nothing of value is possible therapeutically.

The primary lung tumors are much less common. It is important to differentiate those that originate in the bronchi from those that originate in the lung parenchyma. Benign tumors are very infrequent and are usually found at autopsy. In the bronchi they include (1) adenomas which originate in the mucous glands of the submucosa; (2) lipoma and (3) papilloma which are very rare; (4) chondroma, which is usually solitary and may calcify; and (5) osteoma. In the lungs benign growths are curiosities.

The malignant tumors, both of the bronchi and lungs, are, however, much more common than is generally supposed. In the bronchi they include spindle- and round-cell sarcomas and carcinoma. In the lung parenchyma they include (1) carcinoma, which usually begins to grow either at the hilus or near the visceral surface; (2) sarcoma, which usually begins to grow near the hilus; and (3) endothelioma, which originates on the surface of the lung.

The symptomatology of lung tumors shows a general resemblance to that of other pulmonary lesions. One distinguishes a broad group of general symptoms such as those one finds with lesions in general and tumors in particular. As regards the focal signs these differ with the location and gross characteristics of the neoplasm. In the pleural type of growth the symptomatology is very similar to that of a pleuritis with or without an effusion. In the hilus type of tumor the symptoms are those of a chronic bronchitis, bronchiectasis or lung abscess; these neoplasms grow

more rapidly, produce pressure symptoms and form metastases. The symptoms include cough, with or without a profuse expectoration, pain in the side, fever, loss of weight and strength, and the others commonly seen with such diverse lesions as a tuberculosis produces.

Roentgenologically there are nodular and infiltrating types of growth. The former seems to be less common and consists of various sized and distinct masses in the parenchyma and near the roots. Sarcoma is especially apt to extend out along the septum between the upper and middle lobes. Primary carcinoma consists of an infiltrating mass near the root and extending out along the bronchial tree. The characteristics of secondary tumors are the following: Metastatic sarcoma consists of sharply outlined nodules occupying more particularly the parenchyma. Hypernephroma produces a general infiltration of small miliary bodies, sharply defined and extending out from the roots. Metastatic carcinoma occurs as (1) a nodular type of indefinitely outlined fuzzy masses located at the roots and in the parenchyma; (2) an infiltrating type, which is most common, and which begins as a thickening near the hilus and gradually shades off; and (3) a miliary type resembling miliary tuberculosis except that the areas are larger, more dense, and more sharply outlined (lymphangitis carcinomatosa).

The bronchoscope is an important aid in diagnosis. Yankauer has pointed out that 12 per cent of the cases which he has examined through the bronchoscope have had malignant disease. A definitive diagnosis is possible when a piece of tissue can be excised. Similarly positive diagnoses are possible in the cases with pleuritic effusions in which the sediment of the fluid contains tumor cells.

Much experimental work has been done in animals on the removal of one or more lobes of the lung (Sauerbruch, Johns Hopkins group, Rockefeller group). Lung extirpation in animals is technically a simple matter; it is far more difficult in humans. Experimental animals recuperate more quickly because they are not hampered by any preëxisting disease of long standing. Operations have been done successfully in man, although their number is very few.

Access to the interior of the chest is best obtained by the long intercostal incision previously described. As a general rule as soon as one has determined that no metastases are present and that the tumor is technically removable, the portion to be excised is delimited and is tied in sections with a number of chain ligatures; the tissue is divided with the knife or, better still, with the actual cautery. The handling of the bronchial stump is always a matter of difficulty and fistula formation is exceedingly common. For this reason a number of different technics have been devised, all of which aim to avoid this complication; but all of them are uniformly and equally unsuccessful in the same proportion of the

cases. The simplest method—that of securely tying the stump after crushing with a heavy clamp—is the equal of any. The fistula, when it occurs, is best allowed to close spontaneously and in the greatest number it so does. Under such technic a form of air-tight drainage is essential. Healing takes place by granulation and the bronchial stump becomes covered by a mass of scar tissue.

The lung has a rich lymphatic supply and the operability of cases of malignant tumor would naturally be chiefly determined by the situation and extent of the primary tumor and by the amount of metastatic formation nearby in the glands at the root of the lung, or in the lower triangle of the neck, or at distant locations. The latter are specially frequent in the brain, in the suprarenals and in the thyroid gland. The technical difficulties vary with the situation of the tumor: When the tumor is near the surface of the lung, excision is comparatively easy; when the growth is near the hilus the difficulties are many. At the root of the lung there is comparatively more difficulty in securing a complete hemostasis; the danger of postoperative hemorrhage is larger; there is more likelihood of pulmonary infarction. It is advisable and necessary that a sufficient length of main bronchus remain after the ablation of the lobe of the lung to permit a satisfactory closure. Hitherto when the stump of bronchus promised to be too short, it was thought that operation would be impossible; it is to be hoped that a technic will be developed in which operation will be made feasible because of the use of fascia transplanted into the defect in the bronchus which results after the lobectomy. Extirpation of the lower lobes is less difficult technically and is less dangerous clinically than extirpation of the upper lobes.

There are still far too few human cases of radical operation for pulmonary tumor to enable one to formulate any accurate opinion as regards the ultimate possibilities; up to the present all have been fatal (Helferich, Heidenhain and Murphy, Garré, Kummel). Some idea of the possibilities can be perhaps gained by comparison with lobectomy for lung abscess; the best statistics (Lilienthal) available at present show that a successful issue can be expected in about 50 per cent of the cases. If such results are possible with the badly infected lung abscesses, surely much better results can be expected with the comparatively clean cases of lung tumor. In animals the results vary with the skill and experience of the individual worker: In some series the mortality is about 5 per cent; in others it reaches to 85 and 90 per cent. The cause of death in animals includes sepsis and leakage from the bronchial stump. Marked transudations of clear fluid into the pleural cavity occur in one-half of the cases.

When only one lobe is removed the remaining lobes of the lung quickly fill up the vacancy left by the extirpation. When an entire

lung, however, is removed a number of factors contribute toward the obliteration of the cavity. These include: (1) Expansion of the remaining lung with (2) the dislocation of the mediastinal structures toward the operated side; (3) flattening of contraction of the thoracic wall with its attendant scoliosis; and (4) the elevation of the diaphragm. The largest part is played by the heart and lungs. Commonly an enclosed pneumothorax results which in time is aborted coincidently with the obliteration of the cavity; in a few cases the pneumothorax persists for an extraordinary length of time. There is evidence to show that the heart undergoes some hypertrophy.

The removal of one or more lobes of the lung seems to have no effect upon the longevity of animals.

In recent years bronchoscopic technic has improved to such a degree that it has been found possible by Jackson in a particularly favorable case to remove an endothelioma of the bronchus endoscopically. It is to be hoped that the successfully treated cases of this nature will continually increase. One of the dangers, however, which must be remembered is that the bronchoscopic technic gives but a limited field of vision and the visible tumor removed may be a small part of a large growth. Another danger is that a serious and fatal hemorrhage may follow, if an endoscopic removal of a vascular tumor be attempted. Bronchoscopic excisions should only be attempted in the most favorable of conditions.

The bronchoscope permits one palliative procedure which is useful in tumors originating in the bronchi or near the roots of the lung. Commonly bronchiectatic dilatations occur; or the tumor, breaking down and becoming secondarily infected, gives rise to a lung abscess. In either case a most deplorable condition results: The suppurating process, because of its profuse expectoration and most offensive odor, causes the patient to become a nuisance both to himself and his immediate family. For these patients some amelioration is possible by intratracheal and intrabronchial washings through the bronchoscope (Yankauer).

**Mediastinal Tumors.** Primary tumors of the mediastinum are chiefly those originating in the lymph nodes and pathologically are usually the lymphogranulomatous type of tumor—Hodgkin's and lymphosarcoma. It is important to remember that in Hodgkin's disease involvement of the intrathoracic nodes occurs in 25 per cent of the cases. (Wessler). The chief roentgenological characteristics are (1) mediastinal tumor; (2) isolated nodules or tumors in the lungs; (3) infiltrative changes; and (4) discrete nodules at the roots of the lungs. The type most commonly found is type 3, almost always with one of the others.

Patients with far-advanced tumors of the mediastinum lead a wretched existence. Compression of the large vessels—the superior and inferior vena cava—and of important nerve trunks makes

their lives miserable. Owing to the fact that invariably the patient reaches the surgeon in a far-advanced stage of the illness the tumor is inoperable because of technical reasons. What would be possible if these patients were referred to the surgeon at an early and opportune moment still remains to be seen. At the present time all that can be done surgically is of a palliative nature and consists of providing additional room within the bony thoracic cage for the increase in growth of the tumor so that the extreme discomfort can be alleviated. These decompression operations serve a similar purpose to those practised on the skull for the relief of brain tumors. The technic has been developed by Friedrich and by Sauerbruch and consists essentially in dividing the bony chest wall (1) through the middle of the sternum either transversely or better longitudinally, or (2) directly alongside of it. In suitable cases the purpose can be achieved under local anesthesia.

In very late cases considerable dyspnea develops, which is due to compression either of the trachea low down near the bifurcation or of its main divisions near the latter. The marked accompanying cyanosis frequently raises the question of the propriety of doing a tracheotomy; but this is useless for the reason that the point of obstruction is much below the point of attack. The only method available is to intubate the trachea and to insert a rigid catheter below the obstructed area in the bronchus. Conditions are precarious then and death is usually not far removed.

The mediastinum is one of the points of election for the appearance of dermoids and teratomata; the former are cystic and the latter are solid types of growth. They spring from embryonic inclusions. Surgical interference has hitherto been advised only when these seriously interfere with the circulation or with respiration. An excision *in toto* has been successful in only one case. A conservative form of attack is to marsupialize the cyst.

**Tumors of the Heart.** Tumors of the heart are still autopsy findings and are medical curiosities more than anything else. In the present state of knowledge they are beyond the reach of any method of therapy except perhaps the roentgen ray and radium.

*Roentgen-ray Treatment of Intrathoracic Tumors.* The treatment of intrathoracic tumors by radioactive agents—the roentgen ray and radium—is still in an unsettled state. It seems that in order to administer these agents successfully very large doses are necessary both to avoid irritating the tumor into an increase of growth and to cause successfully the death of all of the tumor cells, including especially those situated most distantly. Rays of sufficiently deep penetration are absolutely necessary. The principal difficulties in the technic lie with the safe methods of administration whereby such relatively enormous doses can be exhibited without causing stubborn burns of the skin and necroses of various kinds in the neighboring deep organs. Such excessively large

amounts of radioactive energy directed at any animal body commonly result in an artificial severe anemia and severe collapse which demands the immediate recuperation of the patient by vigorous means including transfusions of blood. Fatalities have occurred. It takes nicety of judgment to gauge the dose of radioactive energy accurately consistent with producing the maximum results with the minimum of damage. Much better work in this regard had been done in the European centers than in this country. A great deal of intensive work is constantly going on which has for its immediate object the avoidance of these difficulties and dangers and the improvement of radioactive therapy.

Tumors of the lung of the types usually found do not lend themselves readily to any beneficent effect from treatment with the roentgen ray or radium. Much better results are obtained with the tumors originating in the lymph nodes. There seem to be better average results in lymphosarcoma than in Hodgkin's disease, but in both the tumors can be caused to shrink and to disappear. Unfortunately, however, these are usually only temporary phenomena and the tumors rapidly recur. Lewis had a case in which a mediastinal tumor recurred three times after the apparent disappearance which followed radioactive therapy; finally the tumor recurred for the fourth time and the condition ultimately proved fatal. In none of these types of tumor does the disappearance of the tumor coincide with any change in the blood findings. It is to be hoped that with continued experience much more knowledge will be obtained which will permit a more effective and lasting disappearance of these tumors.

Where the tumors are accessible, technically operable and can be safely removed with the knife, the latter method is still the preferable one. Otherwise the tumors should be attacked with the roentgen ray or with radium. In operated cases the latter should be employed as a subsidiary measure.

**Esophageal Tumors.** With esophageal tumors one is more fortunate. Owing to the comparative slowness of growth of the malignant tumors of the esophagus—practically always carcinoma—the diagnosis can still be made in most of the cases while the lesion is still confined to the esophagus.

The earliest attempts at esophageal operations made use of the dorsal approach through the posterior mediastinum. The later group of experiments dealt with the transthoracic approach. Experiments were carried out on the cadaver, on animals and in certain instances human operations were also in the nature of experiments. Up to within the last year the method of approach was universally the second.

In dealing with resection of the esophagus it is necessary to remember that besides the excision of the tumor-bearing area provision must be made for the reestablishment of the alimentary



canal. The mobilization of the tube for the length necessary for suture in any portion of the esophagus proper is not possible beyond a distance of perhaps one inch. At the cardiac end of the esophagus the adjacent end of the stomach may be mobilized for a distance of not more than two inches. In either case even when the necessary mobilization is possible the suture line lacks the security present in intestinal suturing by reason of the absence of the peritoneum or of a similar protective structure; leakage almost invariably occurs. Another method must then be available to secure a successful result.

It has been found in actual practice that, owing to the fact that the upper segment leaks always and produces a fatal mediastinitis, it is necessary to remove the esophagus entirely from the chest. This is an extremely hazardous operation and up to the present has succeeded in only one case of Török. Unfortunately it has not been possible for Török or for any one else to repeat this primary success. In the last year Lilienthal has turned from the intrathoracic method of attack to the earlier approach via the dorsal mediastinum and has devised a technic which first seals off the mediastinum and prevents a mediastinitis; secondly, permits the excision of the tumor-bearing area; and, thirdly, permits a plastic operation for the restoration of the continuity of the canal. He, too, has had one successful case, but this again is an isolated instance and it remains to be seen whether this will be repeated by himself or by others before a final judgment is possible. America deserves great credit for having these two successful cases to its record.

The causes of failure with esophageal resections are chiefly shock and infection. The operability of the tumor is determined by the local characteristics of the growth, the presence of glandular metastases, the situation of the tumor, and the adhesions to important structures. A tumor which has perforated is absolutely inoperable because of the danger of infection in the mediastinum. Naturally there are not sufficient data available to enable an accurate judgment as to the actual proportion of operable cases, but it would seem fair to say from one's general experience that about 50 per cent of the cases of carcinoma of the esophagus are in an operable condition when they are first seen by the surgeon.

It is necessary to repeat again and again—even, perhaps, to the point of boredom—that the successful surgery of intrathoracic tumors requires the greatest coöperation on the part of the medical men. Early diagnosis is imperative and early surgical exploration is a *sine qua non* of success. Medical men, too, must bear with the surgeons in the difficulties and disappointments of their early attempts until a satisfactory technic is established which can cope safely with these newer and difficult problems.

# REFERENCES.

1. Blumgarten: *AM. JOUR. MED. SC.*, 1921, 192, 377.
2. Carisi: *Riforma Medica*, 1920, 36, 1124.
3. Du Bray and Masson: *Arch. Int. Med.*, 1920, 26, 715.
4. Eastwood and Martin: *Lancet*, 1921, 201, 172.
5. Gack: *Lancet*, 1921, 200, 1286.
6. Hedblom: *Arch. Surg.*, 1921, 3, 56.
7. Heuer and Dunn: *Johns Hopkins Hosp. Bull.*, 1920, No. 348, 31.
8. Jackson: *Tr. Am. Laryng. Assn.*, May, 1916.
9. Lemon and Doyle: *AM. JOUR. MED. SC.*, October, 1921.
10. Lilienthal: *Ann. Surg.*, 1921, 74, 259.
11. Pallasse and Roubier: *Ann. de Med.*, 1916, 3, 243.
12. Pfahler: *Am. Jour. Roentg.*, 1919, n. s., 6, 575.
13. Warren: *Arch. Int. Med.*, 1911, 8, 648.
14. Warthin: *Med. News*, 1897, 71, 489.
15. Wessler: *Jour. Am. Med. Assn.*, 1920, 74, 445.
16. Widai and Ravaut: *Comp. rend. Soc. de Biol.*, 1900, 52, 648.

## THE DIAGNOSIS AND TREATMENT OF AMEBIC COLITIS.\*

BY ALFRED C. REED, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, STANFORD UNIVERSITY MEDICAL SCHOOL,  
SAN FRANCISCO, CAL.

HORACE GREELEY made a comment worthy of closest scrutiny by medical writers when he said, "I have not time to be brief." In discussing today so broad a subject as the diagnosis and treatment of amebic colitis, and a subject with so voluminous a literature, it would be improper to present other than a clear and condensed outline of the practical matters at issue. For that reason extended historic and literature references will be omitted, laboratory phases will not be discussed and attention will be centered on the practical clinical features of the subject.

Confusion has arisen from the indefinite use of the word dysentery. As employed here dysentery refers to a clinical syndrome of frequent bowel movements associated with pain, tenesmus, and mucus and blood in the dejecta. In this sense dysentery is purely symptomatic and not at all a disease entity in itself. A classification of its causes is easily made and helps materially in clinical study of the patient.

1. Dysenteries of bacterial origin.
2. Dysenteries associated with other definite diseases such as tuberculosis and syphilis.
3. Dysenteries due to toxic substances such as mercury and arsenic.

\* Read before the annual meeting of the Utah State Medical Society, September 15, 1921, Salt Lake City, Utah.

4. Dysenteries due to irritants, as in the orient, chopped pig bristles and bamboo spicules.

5. Dysenteries due to animal parasites. In this group are the dysenteries of kala azar, pernicious malaria and trematode infections. Also are included ciliate and flagellate dysenteries which are of commoner occurrence than ordinarily estimated, and finally amebic dysentery.

Amebic infection is widespread in all hot climates of the earth and has been known in many sections of temperate climates. Due to its wide dissemination it has ceased to qualify as a strictly tropical disease in the last few years. In the United States it is becoming prevalent in all sections. Little is known of its endemic distribution at the present time. Factors which have dealt largely with its recent increase are (1) the return of soldiers after the World War, (2) increased streams of travel and heightened excursions of migratory labor and vagabonds, and (3) influx of foreign population elements into American agricultural and rural districts.

In England, H. A. Bayliss<sup>1</sup> states that amebic dysentery is common and estimates that 6 per cent of the adult males at home are carriers. As early as 1913, H. Z. Giffin,<sup>2</sup> in the middle northwest of the United States, reported 148 cases of *Entameba coli* and 79 cases of *Entameba histolytica* in 1700 persons examined. Reports and clinical experience of amebiasis increased until, in 1920, after examining 2300 returned overseas soldiers and 576 home service men, Kofoed and Swezy<sup>3</sup> recapitulated the situation in the United States in the following terms:

(a) Carriers of ameba in the United States were greatly increased by the return of the soldiers.

(b) There is a larger number of carriers than expected among the normal population.

(c) The dysenteric syndrome is not an essential feature of the disease and infection is by no means limited to the tropics.

(d) Carrier phases are persistent and are possible foci of contagion.

(e) The percentage of carriers relapsing or developing serious sequelæ is unknown.

Without discussion of symptomatology it is still necessary to emphasize some of the characteristic and yet misleading clinical features of chronic amebiasis. The essential lesion in amebic dysentery is an undermining ulceration of the mucosa of the large bowel due to a gelatinous necrosis caused by the invasion of *Entameba histolytica*. The ameba is not found in the necrotic tissue but ahead of it and invading the healthy submucosa. Under

<sup>1</sup> Jour. Trop. Med. and Hyg., October 15, 1920.

<sup>2</sup> Jour. Am. Med. Assn., August 13, 1913.

<sup>3</sup> New Orleans Med. and Surg. Jour., July, 1920, and elsewhere.

conditions favorable for its growth and reproduction the amebæ exist in a vegetative or free-moving form, while under less luxuriant environment they encyst in a resistant resting form.

The difference between chronic amebiasis and the carrier state is relative only. There is no reason for believing that *Entameba histolytica* can inhabit the human colon under any circumstances as a mere harmless commensal. If it is in sufficient numbers and is of sufficient virulence to produce clinical symptoms those symptoms may be of most diverse sort. As the infection increases in quantity and virulence the clinical picture will approach that of true dysentery. On the other hand as the infection decreases in quantity and virulence the clinical picture will be that of the carrier state.

Vegetative amebæ as seen in acute dysentery are extremely vulnerable to all manner of hostile influences and consequently die quickly when they have passed from the human host. Moreover, even if ingested vegetative amebæ die from ordinary contact with gastric juice in the stomach. Invasion of man, therefore, is accomplished solely by the encysted form of amebæ. The resistant cysts are carried to the human stomach through the medium of contaminated food or drink, and are only dissolved and the amebæ set free under the influence of the pancreatic juice. It follows that the subacute and chronic cases and the carriers who present no symptoms, and in all of whom cysts are numerous, are alone to be feared from the standpoint of contagion. Vegetative forms are present in proportion to the acuteness of the disease and cysts are correspondingly absent. Fulminating and fatal cases are free from cysts. Chronic cases and carriers have few if any vegetative amebæ, and then usually only in the presence of diarrhea. In the carrier or chronic case an intercurrent diarrhea, as from a cathartic, will be accompanied by the appearance of vegetative amebæ. In these cases, just as occurs in cholera carriers, there is constant risk of some intercurrent factor causing an exalted virulence of the amebæ, for instance, acute mild intestinal indigestion or any temporary lowering of resistance or vitality.

Chronic amebic infection is frequently accompanied by symptoms of a nature so diverse, bizarre or unexpected that no diagnostic help is afforded and amebic colitis is not even suggested. One or more of the following conditions, for example, may occur: Neurasthenia, physical depression, constipation, recurrences or exacerbations, long intermissions, a surprising absence of bowel disorders, more or less decrease of weight, gastrointestinal complaints of great variety, anemia, pain and soreness in the right lower quadrant, chronic dyspepsia, general ill feeling and nervousness. In the cases seen on the Pacific Coast the latent and atypical course is prevalent. Not infrequently after a general examination has failed to reveal the origin of complaints such as those mentioned

amebic cysts are discovered and the symptoms disappear after appropriate treatment.

It cannot be too strongly emphasized that amebic infection is prevalent in the United States, that acute clinical dysentery is far from being a universal feature of it, and that every patient in whom etiologic diagnosis is indefinite or gastrointestinal symptoms are present should be investigated for the presence of ameba. Two chief vectors are concerned in the spread of amebic cysts in the actual transference of cysts from infected dejecta to new mouths. These are water and flies. Moisture may prolong the life of cysts to a month or more, and cysts may be carried directly through the agency of unboiled drinking water or indirectly through the use of infected water in mouth washes, enemas, douches or in cleansing food. Flies do not carry amebic cysts primarily on their feet, which they clean frequently, but through the medium of infected fecal matter eaten and passed again by the fly. The chief danger, therefore, is from fly droppings.

Diagnosis of amebic colitis rests finally and solely on the presence of vegetative *Entameba histolytica* or its cysts in the dejecta. From a more general point of view two rules can be formulated with safety: The first is to search for amebæ whenever an obscure clinical picture presents itself without definite localization. The second rule is to search for amebæ in every case presenting intestinal symptoms of any sort. Many a patient who has been having his ups and downs for years will clear up when his amebic infection is removed. Under these two general rules diagnosis is much more intimately concerned with thorough routine examination than with discovering a dysentery syndrome. Examination for amebæ should be practised as invariably under these circumstances as examination of the prostate, the rectum and common points of focal infection.

Whenever there is suspicion of colonic disturbance rectal and sigmoidoscopic examination should be instituted at once, and such a routine practice will save many a mistaken diagnosis and many a life. Obviously in a diarrheic or dysenteric condition examination for amebæ and other parasites will be exhaustively prosecuted. Frequently amebæ will be found in direct scrapings from sigmoidal or rectal ulcers or will be found imbedded in mucus secured by the insertion of a soft fenestrated colon tube. In a chronic or latent case microscopic search should include specimens both of a formed and of a liquid stool. The former is more apt to show cysts and the latter, as obtained after salts, is apt to contain vegetative forms. The vegetative forms are more common in the mucus and blood while the cysts are inclined to be found in the firm fecal portions. Negative examinations of three different stools are necessary to establish reasonable certainty of the absence of amebæ. Motile forms should be checked by the dis-

covery of the corresponding cysts. Of the two, cysts are more distinctive than motile amebæ. Herbert Gunn<sup>4</sup> has shown the confusion that may exist between the appearance of pathogenic motile amebæ and that of active fresh leukocytes. This confusion is especially noted in the gall-bladder, bile ducts, abscesses and pus as well as under certain conditions in the colonic contents. A wet smear preparation of normal blood will show these ameboid leukocytes actively motile for many hours. After intensive treatment of amebic colitis the stools should be demonstrated free from amebæ for six months before reasonable assurance of cure is entertained.

The technical methods for the microscopic examination for amebæ are detailed in standard texts and will not be reviewed here. The essential object of the examination is to differentiate the pathogenic *Entameba histolytica* from the relatively harmless *Entameba coli* and *Entameba nana*. More knowledge is required before we can say with finality that these so-called non-pathogenic amebæ are really harmless when they parasitize a human host. So-called cultural or water amebæ are not parasitic for man. Pathogenic properties in amebæ are related apparently to a necessity for living in or on living tissue. Non-pathogenic amebæ feed on waste or other non-living material.

The recently described *Entameba nana* is often distinguished with the utmost difficulty from *Entameba histolytica*. Special training and experience are necessary in order to recognize and diagnose amebic cysts just as is the case with vegetative forms. Only the opinion of a trained parasitologist is worthy of confidence. There is reason for believing that pathogenic amebæ may be modified by varying climatic conditions and personal relations of the host into differentiated species.

In differential diagnosis we must remember that amebiasis can only be determined by the presence of pathogenic amebæ. Returning to the classification of dysenteries we have to consider first those of bacterial origin. These are of two kinds: (a) Those due to some strain of dysentery bacilli; specific agglutination tests, fever and evidence of toxemia are characteristic of these. (b) Dysenteries due to customary intestinal bacteria. Such a primary diagnosis can only be made in the presence of visible ulcerations after scrupulous exclusion of amebæ and dysentery bacilli. Secondarily such a bacterial invasion may follow amebic ulceration and be a potent agent in prolonging the primary lesions. Especially in tropical climates amebic and bacillary dysenteries may be combined, and while improvement may follow specific treatment of the one the patient will not be cured until both have been specifically attacked. It is a principle of tropical practice

<sup>4</sup> California State Jour. of Med., 1921.

that the diagnostician cannot safely rest with the establishment of the first diagnosis arrived at. He must embrace in the technic of his study a review of the entire category of possibilities. This is due to the fact that in chronic and parasitic diseases the diagnosis is apt to be multiple. In no department is this principle more valid than in the diagnosis of dysentery.

Little need be said of the differentiation from amebic colitis of dysenteries of class 2, those due to other specific diseases, such, for instance, as tuberculosis, except to emphasize the constant danger of confusing cancer low in the large bowel with a parasitic dysentery. In temperate climates and in patients over forty years of age, especially if they have not obviously been exposed to parasitic invasion, cancer must be consciously excluded. Chronic amebiasis may be simulated by intestinal tuberculosis, and both are apt to be localized in the cecum and ascending colon.

Dysenteries of the third class, due to toxic substances, are distinguished from amebic colitis by the absence of parasites and by the history and evidences of the causative poison. The same may be said of those due to irritant substances. Dysenteries due to animal parasites other than amebæ depend for their recognition on the discovery of those parasites and recognition of their natural history in man. Combined infections are frequent.

**Treatment.** The treatment of amebic colitis will be discussed from the standpoint of personal experience only. This experience includes two years' work in central China with foreigners and native Chinese as well as the resources of private practice and the Stanford medical wards. No reference will be made to the enormous literature, history and experimentation on this subject. There is a wide divergence of opinion and practice in the treatment of amebiasis, and the surprisingly large number of patients relapsing after various common methods of treatment is the best commentary on their effectiveness. It can be anticipated that some 90 per cent of chronic cases can be cured along the lines here advocated. Further courses of treatment will reduce the remainder. A residuum will be left as ineradicable by any method of treatment, and such cases will usually be found to harbor deep-seated infection in the appendix or other remote focus.

*Acute Amebic Colitis.* In the presence of acute clinical dysentery due to *Entameba histolytica* the stools show abundant vegetative forms and few if any cysts. Emetin hydrochloride should be administered, 1 gr. in one dose hypodermically daily, for six to eight days. Improvement is usually seen at once and clinical cure seldom requires more than three to five days. From the etiologic and symptomatic standpoint no concomitant treatment is required. But thoroughness of treatment is perhaps enhanced and mixed infections better controlled if the patient is kept warm and absolutely quiet in bed on a restricted smooth diet. After

an interval of two to four days the emetin should be repeated in similar dosage for five days. Following this second course the physician is guided by the results of stool examination, and further treatment, if needed, is substantially as detailed below for chronic cases, omitting the first week. Intravenous use of emetin is seldom necessary and is indicated only in fulminating cases.

*Chronic and Latent Amebic Colitis.* In the subacute, chronic and carrier stages motile amebæ become progressively fewer and cysts alone are usually found. In the chronic cyst-bearing amebiasis a course of ipecac in massive doses is sometimes first employed. After a day of absolute rest on regular diet a single dose of 90 gr. of powdered ipecac root is administered in 5-grain salol-coated pills. Opium in some form is given a half-hour previously. If possible this dose is increased to a maximum of 120 gr. In no case is this course prolonged beyond five days. Severe diarrhea is frequent and vomiting may appear at any time. It is a matter of judgment how far to modify the treatment in the presence of these or other complications.

After the ipecac course two days of rest on regular diet are allowed. The second week is inaugurated by 0.3 gram neosalvarsan intravenously. Each day, beginning with the neosalvarsan day, a total of 3 gr. of bismuth emetin iodide is given by mouth in one-grain pills. Each evening of this week a colonic irrigation is given with the patient in the knee-chest position. As near as possible to one gallon of 1 to 2000 thymol solution at body temperature is slowly introduced through a soft short colon tube.

The emetin iodide and colon irrigations are continued for six days, and on the seventh the patient rests. On the first day of the third week 0.9 gram neosalvarsan is given intravenously and the emetin bismuth iodide is continued as before for six days. The daily colon irrigation is continued each evening, using 1 to 2000 quinine solution. A third neosalvarsan completes the third week. The value of the colonic irrigations is sometimes debated, but the thoroughness of the treatment is doubtless enhanced by their inclusion. In place of the bismuth emetin iodide emetin hydrochloride may be employed hypodermically.

After the third week ordinarily treatment is contingent on the recurrence of cysts in the stools, in which case the procedure of the third week should be repeated. Stool examinations should be made at least twice weekly for a month, including both liquid and formed specimens, weekly for a second month, and monthly for two additional months before the case is pronounced clinically cured. At the present time it is doubtful if we can state with certainty when amebic colitis is permanently cured. Lacking ipecac treatment in some form the parasites probably remain permanently in man when once established. While there is a



possibility of amebic parasitism being self-limited, as in the case of hookworm, the point is still uncertain.

The title of this paper does not include discussion of complications of amebic colitis. However, mention must be made of amebic foci in the appendix which are probably responsible for many resistant cases. Many of these, uncured by other treatment, will be cleared by appendicostomy and colon irrigation. But the same result apparently follows appendectomy and surgical removal in this way of the amebic focus. Appendectomy, therefore, should be considered in cases resistant to medical treatment. Biliary tract infection is a possibility worthy of serious consideration.

*Prevention of Amebiasis.* Obviously prevention of amebic infection depends primarily on proper disposal of cyst-infected fecal material. Secondly and more practically it depends on avoidance of ingestion of cyst-infected food and drink. Food infection is favored chiefly by flies and by unclean methods of handling and preparation. Every individual should make it a practice to wash his hands immediately before eating and to keep his fingers out of his mouth at all times. In a broader sense, too, the introduction of pathogenic amebæ by foreign immigration deserves special concern.

*Emetin.* Emetin is a potent and toxic alkaloid and must be handled circumspectly. It causes gastrointestinal irritation, low blood-pressure with a fast, weak heart and depression of the central nervous system. Its toxicity varies with different commercial preparations. The diarrhea produced by emetin may be confused with an uncured dysentery, and serious poisoning result, from pushing the drug too far. Occasionally cases of idiosyncrasy to emetin are seen. It causes considerable local irritation on injection. The use of emetin has been discussed in greater detail previously.<sup>5</sup>

*Conclusion.* In the words of Manson, "The capacity for latency often exhibited by the germs of dysentery is remarkable." Pathogenic amebæ are widely spread in the United States. Because of their tendency to produce carrier and chronic forms the physician should be constantly on the watch. Atypical, unexpected and bizarre symptoms are surprisingly frequent. Diarrhea and dysentery are frequently not present either in the history or present status of patients suffering from amebic colitis. No obscure case has been sufficiently studied until amebæ have been eliminated as a possible cause, and every gastrointestinal case, in its diagnostic routine, should have included a search for these organisms.

<sup>5</sup> Reed, Alfred C.: Boston Med. and Surg. Jour., September 14, 1916.

## REVIEWS.

---

COLLECTED PAPERS OF THE MAYO CLINIC. Edited by Mrs. M. H. MELLISH. Vol. XIII, 1921. Pp. 1318; 392 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

EACH annual volume from the Mayo Clinic since 1914 confirms the opinion expressed in this journal by the reviewer (A. P. C. A.) of the *Collected Papers* of that year to the effect that the Clinic was then entering upon its third and final period of development, a period characterized by an "interest which centers in pathology—the causes and natural course of disease." Only 4 of the 117 articles included in this volume are listed under the heading of technic (first period) and very few relate to the end-results of surgical treatment (second period), whereas the great majority concern themselves with the development and course of disease. In order to further this end, not only have extensive clinical investigations been made but much experimental work on lower animals has been accomplished. Thus the Mayo Clinic now stands for the investigation of disease from the broadest scientific point of view. The articles as a whole are well written, make ample reference to the literature, are splendidly illustrated and in number probably exceed the total product of any other local medical organization.

T. G. M.

---

VITAL FACTORS OF FOODS. By CARLETON ELLIS, Consulting Chemist, and ANNIE LOUISE MACLEOD, Associate Professor of Chemistry, Vassar College. Pp. 391; 12 illustrations. New York: D. Van Nostrand Company, 1922.

THIS book is one of the most complete and comprehensive offerings that has appeared on the subject of vitamins. The first part of the book is taken up with their historical development, followed by a series of chapters on their nature, classification, distribution and stability; while the latter part is devoted specifically to the deficiency diseases, especially from the point of view of the pediatrician. An extensive table on the distribution of vitamins is included in the appendix.

The outstanding feature of the book is its completeness and its magnificent bibliography. The organization of the material also

warrants special comment. The personalities of the authors are, however, completely submerged, and there is a lack of the critical element. The book partakes more of the nature of a collection of abstracts of the work and opinions of the investigators in this field of nutrition, leaving the reader more or less to formulate his own conclusions.

While the book does not present any previously unpublished material, it must, nevertheless, be considered a distinct contribution to the science of nutrition. The investigator will be delighted with the splendid set of references, while the dietitian, the pediatrician, and the general practitioner will find it a ready and up-to-date handbook.

A. J. Q.

THE PSYCHIC HEALTH OF JESUS. By WALTER E. BUNDY, Ph.D., Associate Professor of English Bible in DePaw University. First edition. Pp. 299. New York: The Macmillan Company, 1922.

To most people the mere intimation that the psychic health of Jesus was not normal appears as sacrilege, yet the author has undertaken the task of discussing this subject chiefly in reply to certain articles and books which have been published in German and in French, articles that have pointedly discussed the psychic health of Jesus and in which the authors concluded that Jesus was of unsound mind.

The psychic health of Jesus is discussed by some of his critics under various headings, such as: "Was Jesus an epileptic?" "Was Jesus a paranoiac?" "Was Jesus an ecstatic?" "Was Jesus a fanatic?" None of his critics make mention of the possibility of Jesus having been a sufferer from manic-depressive insanity, despite the fact that there is apparently a clear history of mental disease in his family. His relatives and friends, as recited in *Mark*, 3:21, evidently believed that Jesus was of unsound mind. This verse says, "And when his friends heard it, they went out to lay hold on him: for they said, He is beside himself." On this particular paragraph in *Mark*, Soury has commented as follows: "If Mary and the brothers of Jesus had brought him again into the house of the carpenter of Nazareth, the Galilean prophet would perhaps have ended his life obscurely in some cellar of the paternal dwelling, held by a chain as a Gadarene demoniac." "The Transfiguration," "The Cursing of the Fig Tree," "The Cleansing of the Temple" and Jesus' attitude toward his mother are all additional evidence to those who believe that Jesus was of unsound mind.

The author, in a whole-hearted manner in which his faith is evident, endeavors to refute the arguments put forward by Jesus' critics. The book has an absorbing interest and should be widely read.

G. W.

THE PRINCIPLES OF ELECTROTHERAPY AND THEIR PRACTICAL APPLICATION. By W. J. TURRELL, Consulting Physician, Oxford County and City Mental Hospital. First edition. Pp. 276; 29 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

THIS small book is divided into four parts. In Part I current electricity is discussed; Part II is devoted to the task of explaining the therapeutic action of radiant energy; Part III is concerned with electrodiagnosis; the last subdivision of the book explains the action of electrotherapy and some of the conditions for which it is used and also gives the indications for electrical treatment. This last part has to do largely with the ordinary uses of electricity.

This book, while not an exhaustive treatise, presents the subject in a clear and concise manner and should be of value to anyone who uses electricity in his practice. G. W.

STUDIES IN INFLUENZA AND ITS PULMONARY COMPLICATIONS. By D. BARTY KING, O.B.E., M.A., M.D. (Edin.), M.R.C.P. (Lond. and Edin.), Physician to the Royal Chest Hospital, London; Consulting and Examining Physician to the Church Army Sanatorium for Children Suffering from Pulmonary Tuberculosis, Fleet, Hants. Pp. 88; 31 illustrations. New York City: Paul B. Hoeber, 1922.

THIS attractive little book consists of three studies in influenza made by the author while in charge of the medical division of the County of London (Horton) War Hospital during the late war. The first of these has to do with an outbreak of the epidemic among 150 cases of malaria, the second with the after-effects of the acute pulmonary complications of influenza as revealed by clinical roentgenoscopic and postmortem examinations, and the final one with the disease as it affected the nursing staff (329) of the hospital. Numerous case reports, temperature charts, tables and diagrams of chest physical findings and of roentgenoscopic results are included, and serve to greatly enhance the value of the work. The importance of getting the patients to bed promptly is emphasized and strophanthus is the drug which he believes most helpful when pulmonary complications arise. A plea is made for repeated clinical and roentgenoscopic examinations of pneumonia patients during their convalescence in order to discover in their early stages the various complications which, unless properly treated, may end in chronic fibroid lung disease. The chief treatment advocated for this type of affection is respiratory exercises.

T. G. M.

THE CLINICAL METHOD IN THE STUDY OF DISEASE. By R. M. WILSON, M.B., Ch.B., Consulting Physician to the Minister of Pensions. Pp. 57. London: Henry Frowde, Hodder & Stoughton, 1921.

In the scope of an hour's reading there is presented a brief sketch of the life and works of Dr. Horace Dobell, followed by an interesting discussion of the method of study practised by that eminent clinician of the last century and the conclusions to which his studies led him.

J. H. A.

HYPERPIESIA AND HYPERPIESIS. By H. BATTY SHAW, M.D., F.R.C.P., Physician to University College Hospital and to the Brompton Hospital for Diseases of the Chest. Pp. 191; 11 figures and 53 charts. London: Henry Frowde, Hodder & Stoughton, 1922.

FIFTY cases of hypertension which have come to autopsy furnish the material upon which this study is based. An outline of the history, physical examination and autopsy findings is given in the first section of the book. The remaining sections are devoted to analysis of the preceding findings, deductions which may be drawn therefrom and experiments and speculations concerning the cause of hyperpiesia. Pathologic studies of the injected kidneys by Lawrence and the systolic blood-pressure charts which accompany each case-history constitute an important feature of the work and make it worthy of examination. No chemical tests of kidney function are recorded in connection with any case, although admittedly nephritis and diminished kidney function are of primary importance in connection with hyperpiesia. The omission of these and other modern diagnostic methods detracts seriously from the value of the book.

J. H. A.

SMELL, TASTE AND THE ALLIED SENSES IN THE VERTEBRATES. By G. H. PARKER, Professor of Zoology, Harvard University. Pp. 192; 37 illustrations. Philadelphia: J. B. Lippincott Company, 1922.

SINCE the so-called higher senses, sight and hearing, have so much to do with our mental states many works have appeared summing up our knowledge of those senses at different times; in comparison, the other senses have been quite neglected. The present work is an attempt to fill this need as far as it concerns the chemical senses, senses which have so much to do with the proper

functioning of our alimentary tract. Taste and smell both having receptors of chemical stimuli form a very natural group.

Through human examples the author introduces each sense, both in the morphology of the receptors and in their physiology, finally pointing out the situation as it occurs in other animals. The author's great experience in the comparative physiology of the sense organs particularly well fits him to discuss this aspect of the subject. The concluding chapter of the book includes the relation of one sense organ to another and proposes a terminology to deal with sense organs in general, a terminology more or less familiar to one already acquainted with the work of the author.

The editors of the "Monographs on Experimental Biology," of which this is one of the series, have done well in selecting Professor Parker to present these important subjects. H. S. C.

AN INDEX OF TREATMENT BY VARIOUS WRITERS. Edited by ROBERT HUTCHINSON, M.D., F.R.C.P., Physician to London Hospital and to the Hospital for Sick Children, and JAMES SHERREN, C.B.E., F.R.C.S., Surgeon to the London Hospital and Consulting Surgeon to the Poplar Hospital for Accidents. Revised to conform with American usage by WARREN COLEMAN, M.D., Assistant Professor of Medicine, University and Bellevue Hospital Medical College; Visiting Physician to Bellevue Hospital. Eighth edition, revised and enlarged. Pp. 1029; 88 illustrations. New York: William Wood & Company, 1922.

THIS revised edition is printed on a larger page and plainer type than its predecessor. It is thus unified in all particulars with the two companion volumes of this same series—the *Index of Differential Diagnosis* and the *Index of Prognosis*. It aims to provide the practitioner with a complete guide to treatment in one volume. The list of contributors is entirely British and therefore the suggested methods of treatment are not always in accord with American practice. For this edition revision by the American editor consists in adopting various prescriptions to the standards of the *United States Pharmacopeia*; sometimes he comments on the British text in some added footnotes.

The first volume of this work appeared in 1907. Each succeeding effort has profited by the omissions and mistakes of previous editions; so that the present one reaches the high-water mark. The articles on burns, diabetes, electrotherapeutics, hysteria, mental diseases, neurasthenia and rabies have been rewritten, while new ones on encephalitis, kalaazar, snake-bite, transfusion and the surgical treatment of constipation have been added.

It is, of course, no difficult matter to still find omissions according to American ideas, and it is easy to point out suggestions made

which have no real place in the various therapeutic fields. This would be unfair because the book is primarily written for the British by British and for them it is the foremost work of its kind. It is a book that must be useful to every one who studies or practices medicine, because it offers quickly and briefly the important treatment of all conditions, alphabetically arranged, from abdominal injuries to zomotherapy.

T. G. S.

---

GLANDS IN HEALTH AND DISEASE. By BENJAMIN HARROW, Ph.D., Associate in Physiologic Chemistry, College of Physicians and Surgeons, Columbia University. Pp. 218; 2 illustrations. New York: E. P. Dutton & Company, 1922.

THIS book represents an effort to place before the laity a simple statement of the known facts about the endocrine glands. The author cannot resist the temptation to theorize a little, however, though he is careful to explain that he is doing so. It is the sort of book a clinician, rather than a laboratory man, should have written. The former would not have been so pessimistic about the surgical treatment of exophthalmic goiter, would not have declared that endemic goiter represents a thyroid hyposecretion as "is made evident by the general symptoms that develop," and would have devoted less space to such things as Steinbach's and Voronoff's methods of imparting vigor to the body by operations on the genital apparatus, or grafting.

T. G. M.

---

EPIDEMIOLOGY AND PUBLIC HEALTH. A Text and Reference Book for Physicians, Medical Students and Health Workers. In three volumes. Volume I, RESPIRATORY INFECTIONS. By VICTOR C. VAUGHAN, M.D., LL.D., Chairman of the Division on Medical Sciences of the National Research Council and Emeritus Professor of Hygiene in the University of Michigan; assisted by HENRY F. VAUGHAN, M.S., Dr. P.H., Commissioner of Health of the City of Detroit, and GEORGE T. PALMER, M.S., Dr. P.H., Epidemiologist for the Department of Health of the City of Detroit. Pp. 688; 83 illustrations. St. Louis: C. V. Mosby Company, 1922.

WHEN the reviewer received this book he anticipated no special pleasure in the reading of it, but the first paragraph of the preface, in which the author tells of the vivid impression made upon his boyhood mind by the recurring epidemics of "bloody flux" in Missouri, and the subsequent paragraphs in which he relates in brief outline his vast personal experience with epidemic disease, were sufficient assurance that not only might one expect a presentation based upon and tempered by a knowledge gained at first

hand, but one that emanated from a large human interest. In both of these respects this first volume proves itself a complete success.

It is far more than a mere accumulation of statistical data on epidemic disease, though in this regard alone it is of great value, for it brings into permanent and orderly form much important matter from our recent war experience. But besides this the history of epidemic disease, which is always interesting, is dealt with, and also the symptomatology and pathology. Furthermore, the authors have emphasized their personal views in regard to the phenomena of infection, and this in itself tends to give to the book a decided point of view. This is evidenced by the heading for the first chapter—Albuminal Diseases. Other chapters are devoted to individual diseases, as measles, influenza, tuberculosis, etc. Consequently the treatise is of great value to internists generally, as well as to those especially interested in public health. The tables and charts are well prepared and most illuminating. The reviewer will eagerly await the subsequent volumes.

T. G. M.

**STUDIES IN NEUROLOGY.** By HENRY HEAD, M.D., F.R.S. In two volumes. Pp. 832; 182 illustrations. Oxford Medical Publications, Oxford University Press, 1920.

THIS scholarly work is in two volumes and is essentially a republication in an orderly review of a series of seven papers published from 1905 to 1918 inclusive by the author in conjunction with W. H. R. Rivers, James Sherren, Gordon Holmes, Theodore Thompson and George Riddock. No material change has been made in the arrangement of the papers, as each of them deals with a definite theme and is concerned with some distinct aspect of the functions of the nervous system. The author has also added an introduction and an epilogue dealing with the common aims which underlie the various researches, and an appendix dealing with some of the most serious criticisms of the researches on the functions of the peripheral nervous system.

The two volumes are noted for the extreme care and precision used in testing the sensory tracts of the peripheral nervous system, the spinal cord and the brain. The author submitted himself to an experimental section of a cutaneous nerve of his arm and subsequently made many very careful and consecutive notes concerning the resultant sensory changes and those consequent upon the gradual regeneration of the nerve. The first volume is devoted to a discussion of the methods of examination and their trustworthiness particularly as applied to the peripheral nervous system. The second volume deals principally with the spinal cord and the brain and particularly with those sensory disturbances resulting from cerebral and spinal cord lesions.



The book is one of the most scientific and trustworthy that has appeared on the market in recent years and while it advocates no new departure from the realms of organic neurology, it sheds much new light on many obscure facts concerning cerebral and spinal localization, especially as viewed from the angle of the doctrine of evolution. The authors trace physiologic processes produced by various physical stimuli from their origin at the periphery of the nervous system to the moment when they excite sensation.

The leading principles which have emerged from these researches are:

1. When any level of activity is attacked the most complex functions, and those which have appeared most recently in the scheme of human development, are the first to suffer.

2. The negative manifestations of a lesion appear in terms of the effected level, and a negative lesion produces positive results by releasing activities normally held under control by the functions of the affected level.

3. The functions of the central nervous system have been slowly evolved by a continuous process of development.

4. Integration of function within the nervous system is based on a struggle for expression between many potentially difficult physiological activities.

5. Primitive sensation was probably a condition of "awareness" endowed with but slight qualitative or discriminative characters.

The book may be considered as a classic of its kind and is a valuable addition to the library of the neurologist. F. H. L.

VENEREAL CLINIC. By ERNEST R. T. CLARKSON, M.R.C.S., London Hospital. Pp. 456; 35 illustrations, 20 plates (10 in color). New York: William Wood & Company, 1922.

IN the wealth of books of this character, at present on the market, it hardly seems possible to expect anything new. Yet the author has given it to us, not essentially in the material contents, but in the presentation of his subject. Covering only the two diseases, gonorrhea and syphilis, he has presented the subject-matter: (1) As seen in their most frequent manifestations; (2) as though demonstrating individual cases at a clinic; (3) by closely correlating the symptoms with the known pathology and reasons for certain treatments, and enhancing the value of the whole by appending a splendid series of chapters on the sociology and administration of clinics and city health measures. He has written for the "elementary student" and the practitioner taking charge of a venereal clinic: to both we take pleasure in warmly recommending the book, judging it to be safe in its advice, clear in its presentation of the subject and easy of ready reference, with many additional features not found elsewhere. A. R.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**Megacaryocytes in Circulation.**—MINOT (*Jour. Exper. Med.*, 1922, 36, 1) reports the finding of megacaryocytes (megalocaryocytes) in the peripheral circulation of many cases of myelogenous leukemia and in two cases of polycythemia vera, one of lobar pneumonia, one of Hodgkin's disease, and one of sepsis. In all of these cases, except some of the myelogenous leukemias, the blood showed increase of platelets with bits of megacaryocyte cytoplasm and often many immature cells of both the red and white series. The author concludes that the presence of megacaryocytes in the peripheral circulation is indicative of a bone-marrow under intense strain.

---

**The Blood Sugar After Removal of the Liver.**—MANN AND MAGRATH (*Arch. Int. Med.*, 1922, 30, 73) report their observations on the blood sugar in hepatectomized dogs as an interesting phase of their studies on the physiology of the liver. The technic of the removal of the liver includes, first, a reverse Eck fistula and, at the second operation, the ligation of the portal vein at its entrance into the liver, the third operation allowing the removal of the entire liver. Following the operation the animal remains "normal" for three to eight hours and then passes through a series of symptoms—muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitchings, convulsions and death. The average animal dies within two hours after the appearance of the first signs of muscular weakness. The authors point out that the blood sugar begins to fall immediately after operation and its fall to a certain point (0.06—0.04 per cent) is always

accompanied by the onset of the symptoms described. At the time of death the blood sugar rarely exceeded 0.03 per cent. The glycogen content of the muscle decreases coincidentally. Similar studies were made on animals of different species—dog, goose, turtle and fish. In each species investigated removal of the liver produced a marked decrease in blood sugar. The relationship, they conclude, of the decrease in blood sugar and the development of the characteristic symptoms seems to be one of cause and effect.

---

**Capillary Blood-pressure in Arterial Hypertension.**—BOAS AND FRANT (*Arch. Int. Med.*, 1922, 30, 40) find that hypertension cases fall into two groups, (a) those with normal capillary blood-pressures, and (b) those with high capillary blood-pressures (21–70 mm. of Hg). They agree with Kylin that it is possible that the patients who exhibit high capillary pressures are suffering from a general capillary disease with a glomerulonephritis as one of the manifestations, although they point out that it is difficult to see how disease of the capillaries themselves would lead to a high capillary pressure, particularly when arteriosclerosis of itself does not lead to a high arterial pressure. In cases of essential hypertension the capillary pressure is low. They find that in patients with high capillary pressure the variation in different capillaries of the same patient is twice as great (36.6 mm. Hg) as in patients with normal capillary pressure (18.0 mm. Hg). They also conclude that the variability of the capillary pressure depends on physiologic as well as anatomic moments.

---

**Studies on Blood Cholesterol in Syphilis.**—McFARLAND, (*Arch. Dermat. and Syph.*, 1922, 6, 39) has studied the cholesterol content of the blood in a number of syphilitic patients and finds that in general the values are medium and low rather than high. The cholesterol determinations, done by the Bloor method, are, with the possible exception of cases of cerebrospinal syphilis, about the same as in a similar series of non-syphilitic individuals. In cerebrospinal syphilis the percentage of high values was 33.3. The possible relationship between the cholesterol values and the Wassermann reaction, the type of syphilis, and the clinical response to treatment were also studied with negative results. It is of particular interest to note that the positive Wassermann reaction depends in no way on the concentration of cholesterol in the blood. The blood of patients under treatment was also studied with the idea of determining the possible effect of arsphenamine. Here again no significant variations were noted.

---

**The Role of Agglutination in the Immediate Toxic Effects of Arsphenamine.**—OLIVER and YAMADA (*Jour. Pharm. and Exper. Therap.*, 1922, 19, 393) in a series of interesting experiments on animals demonstrated that when single large lethal doses of arsphenamine are given, a characteristic anatomical finding is present in animals at autopsy. This consisted in marked agglutination of the blood from the inferior vena cava, which is definitely shown not to depend on coagulation; as a result of this phenomenon, embolism of small vessels and capillaries throughout practically all the organs and particularly in the lungs. They were also able to demonstrate that rabbits died acutely from the intravenous injections of red cells previously agglutinated by arsphen-

amine in vitro, in which the arsphenamine content was much too low to have caused symptoms. The clinical and anatomical phenomena in these animals were precisely the same as in animals killed with a single large dose of the drug. Similar reactions of a less extent occurred after large sublethal doses of arsphenamine and after small repeated doses. They call attention to the fact that sudden death in the animal depends on the almost complete stoppage of the pulmonary capillaries by embolism and that this in turn causes an acute dilatation of the right ventricle. They suggest that certain of the similar reactions observed in human beings may be due to the intravascular agglutination of the red cells and the consequent multiple embolism.

---

**A Serological Study of Hemolytic Streptococci.**—GORDON (*Brit. Med. Jour.*, 1921, 1, 632) has studied by means of agglutination and absorption tests hemolytic streptococci derived from a variety of sources with special reference to the organism concerned in scarlet fever. It is found that of a large group of streptococci, 93 per cent fell into three main serological types. Of special interest was the fact that in the scarlet fever cases all but two strains were identical and these two strains were different from those obtained in ordinary pyogenic conditions. These observations confirm the work of Bliss and of Tunncliffe and raise the question of whether the streptococcus may not really be the actual cause of scarlet fever. Its constant presence even early in the disease, and the fact that if one eliminates the streptococcus and its associated rash very little remains from which to make a diagnosis, are very suggestive.

---

**Remote Prognosis in War Nephritis.**—DYKE (*Quart. Jour. Med.*, 1922, 59, 207) analyzes the present condition of 100 patients whom he observed in the acute stage of war nephritis four and a half years ago. All had been typical cases of acute nephritis with edema, albuminuria, and hematuria. His observations have a significant bearing on the problem of nephritis in civil life. Of 100 patients followed, 3 are dead, 1 is a complete invalid, 17 are partial invalids with pensions of 20 to 60 per cent, and 79 are "fit." Most of these now found to be fit for duty were completely recovered within twelve months of the onset of the acute disease. Most of those not fully recovered within twelve months have persistently shown signs of nephritis, which by this time is of the chronic type. Eleven patients recovered more slowly and although invalid at one year after the onset have since so far recovered as to be capable of full duty. No symptom or sign (including uremia) occurring during the acute stage of the disease was found to be a reliable guide to its remote prognosis.

---

**Radium Emanations in Exophthalmic Goiter.**—TERRY (*Jour. Amer. Med. Assn.*, 1922, 79, 1) used radium emanations in extremely toxic cases of exophthalmic goiter in an attempt to convert them into better risks for surgical procedures. The emanation tubes were introduced into the gland under local anesthesia. Two patients with high metabolic rates recovered completely after radium alone. Other cases were so far improved as to be favorable subjects for operation. The adhesions which are reported to follow preparatory treatment with the roentgen-ray were not observed in patients treated with radium.

## SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

**Thoracoscopy in Surgery of the Chest.**—JACOBÆUS (*Surg., Gynec. and Obst.*, 1922, 34, 289) says that for diagnosis and localization of pleural and pulmonary tumors it is of great importance to make a roentgen-ray examination before as well as after the induction of pneumothorax. By making a roentgen-ray examination after the induction of pneumothorax, valuable information is obtained which completes the information already obtained by the roentgen-ray examination before the induction of pneumothorax. Thoracoscopic examination gives valuable information in diagnosing and localizing pleural and pulmonary tumors and verifies the roentgen-ray examination. If it is not possible to use a pressure difference apparatus, it might be advantageous to induce pneumothorax previous to operation in the pleural cavity. If a pressure difference apparatus be employed, then pneumothorax for the thoracoscopic examination ought to be induced as shortly before the operation as possible, in order that the inflation of the lung after the operation may not be rendered more difficult or impossible. If the lung is inflated after the operation, more favorable conditions for the course of healing are eventually obtained.

**Gross Pathology of Brachial Plexus Injuries.**—ADSON (*Surg., Gynec. and Obst.*, 1922, 34, 351) says that injuries of the brachial plexus are chiefly situated in the vicinity of the intervertebral canal proximal to the brachial trunk. The injuries may be slight, lacerating only the fascia around the cervical roots or they may be severe and result in laceration of the cervical roots between the cervical ganglion and the cervical trunk with or without avulsions of the ganglion. Inasmuch as injuries of the brachial plexus are produced in the root or the ganglion, they seem primarily to be lesions of the nerve rather than secondary to lesions of the shoulder joint. Patients with milder injuries may be expected partially or completely to recover without surgical treatment, but those with more severe injuries rarely recover even with surgical treatment.

**Surgical Anatomy of the Trigeminal Nerve.**—KANAVEL and DAVIS (*Surg., Gynec. and Obst.*, 1922, 34, 357) say that the distance from a point upon the inner surface of the squamous portion of the temporal bone opposite the petrogenoid tubercle to the foramen spinosum was found to average 2.47 cm. There are six distinct types of middle meningeal arteries, the larger percentage of which give off single anterior and posterior branches. The distances from the foramen

spinosum to the Gasserian ganglion, foramen ovale and foramen rotundum respectively are 1.66 cm. at an angle of 20 degrees occipital from a transverse diameter through the foramen spinosum. In 41 per cent of the cases a marked bony prominence overhangs the foramen spinosum which leads to difficulty in elevating the dura mater and ligating the middle meningeal artery. Further, in 38 per cent marked lateral grooves are present which may lead to difficulty in localization of the operative field. An attempt should be made to save the motor root which lies medial to and somewhat superior to the sensory root centralward from the ganglion. A thin membrane lies between the Gasserian ganglion and the carotid artery in 40 per cent of the skulls examined. The cause of the paralysis of the seventh nerve which infrequently occurs cannot as yet be definitely stated.

**Secondary Parotitis.**—LYNN (*Surg., Gynec. and Obst.*, 1922, 34, 367) says that more attention should be paid to the condition of the mouths of our patients before and after operation. Following operations some mild salivary stimulant should be given to keep the ducts clean. The reason the sublingual and submaxillary glands are practically immune is because they are mucous glands, mucin inhibiting bacterial growth. Furthermore, the parotid is the only salivary gland containing lymph glands. These favor the collection of inflammatory agents. There are two main sources of infection: through the blood or lymph stream and by way of Stensen's duct.

**A Study of Sixty-five Cases Seeking Relief After Short-circuiting Operations.**—SPRIGGS and MARXER (*Brit. Med. Jour.*, April 15, 1922, p. 546) say that about half the patients who sought relief after gastroenterostomy recovered from their symptoms or improved greatly with lapse of time and suitable medical treatment. In most of the remainder a detailed investigation showed abnormalities which are capable of relief by further operation. The conditions which call for a second operation are the persistent failure of medical treatment and inability of the patient to lead a normal life; particularly if it can be demonstrated that bile is regularly in the stomach or that the stoma is not in the lowest part, causing accumulation of food between the stoma and the pylorus, or that the jejunal loops are not normal in appearance, or that there is dilatation of the duodenum and regurgitation of bile, or if there is evidence of ulceration in the neighborhood of the stoma or of active ulceration of the stomach or duodenum. Except for structural disease, short-circuiting operations upon the colon should not be performed unless suitable and persistent medical treatment has failed and sound scientific reasons can be put forward for believing that the operation will benefit the patient. In all cases of chronic alimentary disease, treatment and especially operative treatment should not be undertaken until the case has been investigated as thoroughly as the circumstances permit.

**Ascending Infections of the Kidney.**—WALKER (*Lancet*, April 8, 1922, p. 681) says that organisms may also reach the kidney by the lymphatics surrounding the ureter and between its muscular coats, although the blood-stream is the commonest route. The kidney capsule is an

important link in this lymphatic chain and is the situation in which organisms are most consistently found in cases of ascending infection. In early cases of lymphatic infection of the kidney no organisms are found in the urine. There are reasons to believe that a tuberculous infection of the kidney may take place along a route precisely similar to that followed by pyogenic organisms.

**Gastric Syphilis.**—GALLOWAY (*Brit. Med. Jour.*, February 11, 1922, p. 217) says that there are two symptoms and three signs. The symptoms are, first, anorexia—no other condition shows this so absolutely excepting in some early cases of malignant disease, and secondly, the nature of the pain. The signs are, first, enlargement of the liver (and occasionally also of the spleen) with smooth outline, present in three-fourths of all the cases; secondly, rapid development of cachexia; and thirdly, stigmata of syphilis. The real test is the empiric, the therapeutic, and that may be applied both from its negative and positive aspects. The change is immediate upon specific treatment, while the result is *nil* upon mere careful arrangement of diet and usual drugs.

**Nature and Cause of Old-age Enlargement of the Prostate.**—WALKER (*Brit. Med. Jour.*, February 25, 1922, p. 297) says that it is impossible to explain enlargement of the prostate by any theory of chronic inflammation alone. Although the enlargement may reproduce conditions favorable to the development of a neoplasm, the enlargement itself does not come into the category of true tumors. The condition is in the nature of a fibroepithelial degeneration which finds its analogy in the female in serocystic disease of the breast. This degeneration may be regarded as an accident occurring during the progress of involution of the genital tract. The cause that determines the onset of the condition is unknown, although it is not improbably connected with a loss of endocrine balance occurring during this period. Prostatic enlargement shows a definite distribution that is anthropological rather than geographical in character. It very rarely occurs among Mongolians and negroes.

**Anomalous Abdominal Membranes.**—TAYLOR (*Ann. Surg.*, 1922, 75, 513) says that anomalous membranes are present in from 15 to 20 per cent of newborn infants. They result from atypical peritoneal fusion during fetal life. Many of them are probably modified by later pathological changes due to continued traction, irritation or low-grade inflammation. They occur in the hepatoduodenal region, at the duodenojejunal angle and about the cecum, ascending colon, hepatic flexure and beginning transverse colon. They cause mechanical disturbances, fixation, angulation, compression and torsion of the digestive tract, resulting in partial, continuous and often increasing obstruction. This, in turn, frequently causes dilation proximal to the obstruction. Symptoms result when the obstruction becomes greater than the peristaltic efficiency can easily overcome, independently of time of life. The symptomatology consists of digestive disturbances, general nutritional disturbances and nervous debility. There are usually tender spots in the mid-epigastrium, over the appendix, over cecum and ascending colon and over the duodenojejunal angle, depending upon the

presence of the various lesions. Examination of gastric contents and stools gives no evidence of value as a rule. Good series of plates from barium gastrointestinal studies are likely to show hepatoduodenal membranes, duodenojejunal angle obstructions and pericolic membranes.

**Clinical Aspects of Abdominal Tuberculosis.**—MORLEY (*Brit. Med. Jour.*, March 11, 1922, p. 383) says that pain, when it occurs in recurrent, well-defined, colicky attacks, especially if they return with regular periodicity and sharp intensity, signifies a mechanical interference with intestinal peristalsis and this can be relieved only by operative measures. Glandular masses in the mesentery, if not too extensive and if they do not yield rapidly to constitutional treatment, should be excised and this is particularly urgent when they are associated with colicky attacks of pain. Palpable masses in the ileocecal region associated with signs of chronic intestinal obstruction are an emphatic indication for laparotomy and resection of the tuberculous ileocecal region should such be found. The ascitic form of tuberculous peritonitis is essentially a disease for surgical treatment. The operation is free from danger and its beneficial results are usually dramatic. Finally, in the plastic type of tuberculous peritonitis, if the trouble does not yield to the ordinary medical measures, operation may be undertaken with a fair degree of safety provided that no extensive attempt is made to separate adhesions and there is some ground for hoping that even these apparently desperate cases may make a complete recovery.

**The Treatment of Surgical Tuberculosis with the Carbon-arc Lamp.**—SAUER (*Ann. Surg.*, 1922, 75, 400) says that the treatment consists in placing the patient before the light and exposing the affected part and as much of the surrounding area of the body as possible. About eight to ten hours after the first treatment a deep erythema is noticed. It is as effective as the natural sunlight and has the advantages of convenience and independence of the weather. It is just as effective, if not more so than the roentgen ray without the attendant dangers. It is far more effective than the quartz-mercury vapor lamp, as has been amply demonstrated by Reyn.

**Tuberculous Abscesses of the Chest Wall.**—ARCHINCLOSS (*Ann. Surg.*, 1922, 75, 406) says that tuberculous abscesses of the chest wall are frequent enough to be of importance to the general surgeon, yet rare enough for many surgeons not to have had enough cases for study as to their pathogenesis and treatment. There is a widespread opinion that such cases are due to a "tuberculous rib" as the distributing or primary focus. From this study the lungs, pleura and the mediastinal lymphatics seem preëminently responsible. The abscess is frequently deep as well as superficial to the chest wall. The abscesses occur chiefly on the anterolateral aspects of the chest wall rather than posteriorly. The associated tuberculous lesions are varied in number and importance. They may be or may not be more important than the abscesses. An extraordinarily large amount of calcium deposit may be present. Complete excision of the tuberculous focus, leaving vascular, well-nourished walls to come together, is the treatment; this may have to be modified by an associated lesion.



## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**Acute Infectious and Contagious Diseases in Childhood in the Etiology of Cardiovascular Disease in the Adult.**—SIEGEL (*Arch. Pediat.*, 1922, 39, 314) reviews data collected in the examination of recruits for army service. In a series of 74,130 examinations, 6034 were given detailed cardiovascular examination, and 297 were rejected as unfit because of cardiovascular abnormalities. The histories of the last group were taken with special attention to determining the occurrence of measles, pertussis, scarlet fever, diphtheria, rheumatism, chorea, tonsillitis, growing pains, typhoid fever, dysentery, pneumonia, malaria and syphilis. The cardiovascular abnormalities found in the 297 cases rejected occurred as follows: Hyperthyroidism in 99 cases; combined valvular lesions in 61; functional cardiac disorder in 47; mitral stenosis in 35; mitral insufficiency in 20; aortic insufficiency in 10; cardiac hypertrophy in 10; tachycardia, auricular fibrillation, and aortic syphilis in 4 each; bradycardia, auricular flutter, and congenital heart lesion in 1 each. The etiological factors giving rise to these lesions follow in the order of frequency of incidence: Measles in 61.6 per cent; pertussis in 41.75 per cent; rheumatism in 41.4 per cent; tonsillitis in 36.4 per cent; growing pains in 25.3 per cent; pneumonia in 17.8 per cent; typhoid fever in 16.2 per cent; there was no history obtainable in 14.1 per cent; scarlet fever in 12.8 per cent; diphtheria in 11.9 per cent; dysentery in 11.1 per cent; and chorea in 5.4 per cent. It seemed that diseases causing the gravest constitutional symptoms in this series showed a lower incidence of cardiovascular damage than those in which the constitutional reaction was milder, and in which the patient is either ambulant or in bed for comparatively a short period. This would seem to indicate the danger to the circulatory apparatus following an infectious disease and should emphasize the need of keeping children, ill with these diseases, at rest not only during the period of the acute attack, but also in the post-acute stage, until the circulatory system has returned to its normal state. This should considerably aid in the avoidance of permanent damage to the circulatory system.

**Results of Active Immunization with Diphtheria Toxin-antitoxin in the Public Schools of New York City.**—ZINGHER (*Jour. Am. Med. Assn.*, 1922, 78, 1945) reports that the immunity response to the same mixture of toxin-antitoxin varies greatly in different groups of children. A preliminary stimulation of the tissue cells in Schick-positive children caused by repeated exposure to infection with the diphtheria bacillus seems to enable the cells to give a better response to injection of toxin-antitoxin than in other children whose cells have not been previously stimulated by such exposure. This is the case even though these

exposures have been slight and have not been apparent in the form of a perceptible increase of antitoxin in the circulating blood. After a first series of toxin-antitoxin injections, the immunity responses to the second series did not follow the same inverse ratio noted between original susceptibility of the children in a school and the percentage of successfully immunized children in the same school. Three doses of toxin-antitoxin, each from 1 to 1.5 cc, injected at intervals of one week give much better immunity results than two doses of the same amount injected one week apart. A longer interval between the injection of the toxin-antitoxin has the advantage of allowing the local reaction to disappear more completely before the next injection of toxin-antitoxin is given. There may also be a better antitoxin response when the injections are given two weeks apart. At least six months should be allowed to elapse after the injections of toxin-antitoxin before the Schick retest is made to determine accurately the development of an active immunity. A second series of two or three injections of toxin-antitoxin should be given to those who have not become immune after the first series. There are a few children who fail to develop immunity after toxin-antitoxin injection even after they are given several series. In the schools reported, from 70 to 93 per cent of children were rendered immune after two series of toxin-antitoxin injections. There is practically no danger from anaphylaxis either in repeating the injections of toxin-antitoxin or in giving toxin-antitoxin after a preliminary injection of antitoxin.

---

**The Food Requirements of Children: Fat Requirement.**—HOLT and FALES (*Am. Jour. Dis. Child.*, 1922, 23, 471) say that many of the functions of fat in the diet are still subjects of debate. A certain amount of fat should be supplied to provide fat-soluble vitamin. This amount is not yet known. It may be exceedingly small, but until this is known it seems wise not to reduce the fat supply greatly lest there may be a deficiency in vitamin A. Fat probably has an important influence on mineral metabolism, especially on calcium metabolism; for the best absorption of calcium they have found it desirable to supply as much as 3 gm. of fat per kilo in the early years and as much as 2 gm. per kilo after six years. Fat is probably necessary for proper digestion and utilization of protein and on this account it seems desirable to supply as much fat as protein in the diet. Fat helps to maintain normal physical, bacteriological, and chemical conditions in the intestine. It also exerts a protective action against the irritating effects of the products of carbohydrate fermentation. A great reduction in fat in the diet increases the susceptibility to infection, especially to tuberculosis. The nursing infant receives a generous amount of fat, usually as much as 4 gm. per kilo daily. The infant taking modifications of cow's milk usually receives about 3.5 gm. per kilo daily. Older children studied by the authors took on an average over 3 gm. per kilo when under six years of age, and about 3 gm. per kilo during the remainder of the growth period. The grounds for the current impression regarding the harmful effects of fat on children should be investigated carefully. There seems to be little evidence that a liberal amount of fat in the diet is harmful to children with normal digestion and much evidence that fat is an important and necessary component of the diet during the

entire growth period. In general, it seems rational to supply in the diet of the child as much as 4 gm. per kilo daily at one year, decreasing to about 3 gm. per kilo at six years, and maintaining this value throughout the remainder of the growth period.

**Milk Ingestion in Relation to Changes in Body Weight of Newborn Infants.**—ADAIR and STEWART (*Jour. Am. Med. Assn.*, 1922, 78, 1865) found that the average body weight for 149 first-born and also for 149 later-born infants, whose birth weights ranged between 2500 and 5000 gm., decreased to a minimum on the fourth day, counting the date of birth as the first day. The average loss amounted to approximately 8 per cent of the birth weight for the first-born infants and to approximately 6.4 per cent for the later-born infants. There was no progressively uniform daily decrease in weight; for each group the greatest loss occurred on the second day. Following the fourth day the average body weight for each group progressively increased. On the tenth day, however, the average weight of the first-born and of the later-born was still 2.4 and 2.6 per cent respectively below the initial weight. For each group of babies the greatest daily gain in weight occurred on the fifth day after birth. For the first-born infants of both sexes the amount of breast milk obtained increased rapidly from an average of 13.0 gm. per feeding on the second day to 54.9 gm. on the fifth day. From the sixth to the tenth day inclusive the increase continued, although less rapidly, the average meal on the tenth amounting to 78.4 gm. With the later-born infants of both sexes the average amount of milk per feeding increased from 16.9 gm. on the second day to 59.4 gm. by the fifth day. On the tenth day the food intake averaged 84.7 gm. per feeding. Throughout the period studied the babies of multiparous mothers averaged larger feedings than the babies of primiparous mothers. The heavier infants in general obtained more milk from the breast per feeding than the lighter ones whether first or later born, particularly after lactation was well established. Of each weight group the average meal in general was larger for infants of multiparous mothers than for those of primiparous mothers. Except for the eighth and ninth days, the average amounts of mother's milk taken daily for each kilogram of body weight was slightly higher for later-born than for first-born infants. The average amount of 10 per cent lactose solution taken per feeding increased to a maximum on the second day. On the following three days, as the supply of milk increased, the lactose solution ingested progressively decreased. There was no apparent difference in the amount of lactose solution taken during this period by the later-born as compared to the first-born babies.

**Observations on the Heart in Mothers and the Newborn.**—SMITH (*Jour. Am. Med. Assn.*, 1922, 79, 3) found by clinical, cardiographic and radiographic examination that pregnancy in itself does not cause cardiac enlargement. Such evidences of cardiac enlargement as may be present in the expectant mother under certain circumstances of examination are shown to disappear under other circumstances. Cardiac enlargement in the latter half of pregnancy may be simulated by the upward pressure of the gravid uterus upon the heart, causing cardiac displacement. There are no heart affections which are characteristic

of, or incident to, pregnancy. While pregnancy in all likelihood throws a load of some degree on the heart, the heart is fully capable of adjusting itself to this as it is to other physiologic demands. A definite history of previous infections requires that the expectant mother be closely observed as pregnancy advances for symptoms of masked heart disease, which may not become apparent until brought to light by the heart load of pregnancy. Focal infections may cause symptoms of heart embarrassment in pregnant patients which might erroneously be attributed to pregnancy. Definite cardiac indications for the interruption of pregnancy are rare. Even frankly diseased hearts will exhibit a surprising adaptability to the physiologic demands of pregnancy. The right side of the heart is enlarged in the newborn. Evidence of cardiac enlargement persists for five weeks or longer before the baby's record begins to assume adult characteristics. The heart following birth is frequently irregular at intervals during the first week. Such irregularities may be expected to disappear at a later date and are not indicative of cardiac pathology. Graphic records suggest that it may be possible for maternal irregularities to be transmitted to the child. In a stillborn baby evidences of heart activity were observed for three hours and twenty-four minutes following stillbirth. Massage of the heart through the chest wall may prove to be a useful adjunct to other methods of resuscitation of the stillborn.

---

**The Severe Blood Diseases of Childhood.**—POYNTON, TURSFIELD and PATERSON (*Brit. Jour. Child. Dis.*, 1922, 19, 57) in discussing types of severe blood diseases take up a consideration of von Jaksch's anemia or anemia pseudoleukemia infantum. They group four of their cases under this heading. The criteria which they have adopted are that the child should be under four years of age, that the anemia should be severe, that there should be an unusual proportion of myelocytes present in the peripheral blood, and that the spleen should be of considerable size. In addition, though not invariably present, normoblasts and megaloblasts are commonly found in the films of the blood. Judged by these standards three of these four cases undoubtedly belong to the category of von Jaksch's disease, but the remaining one was doubtful. In this patient the hemoglobin was unusually high and the proportion of myelocytes was unusually low, nor had the spleen such a size as is usually associated with the disease. The erythrocyte count was higher than is expected and the improvement was exceptionally rapid. The general appearance of the patient coupled with the appearance in the blood of myelocytes, normoblasts and megaloblasts led them to believe that this was an example either of a comparatively late stage in convalescence from the disease, or possibly an example of unusually mild degree of the affection. They admit that such a case affords some support to the argument of those who believe that von Jaksch's anemia is not a clinical entity, but an unusually severe stage of any infantile anemia, the uncommon features being merely an expression of the severity of the intoxication. Of the three cases two recovered and one died. Postmortem examination showed petechiae in many organs, an old blood-clot in the pelvis of one kidney, general moderate enlargement of the lymphatic glands and hypertrophy of lymphoid tissue of the body, and a large firm spleen with marked fibrosis.

## OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

**Chemical Observations on the Toxemias of Pregnancy.**—DE WESSELOW, chemical pathologist to St. Thomas Hospital, London, contributes *Jour. Obst. British Empire*, 1922, 29, a very interesting paper upon this subject. At the present time it is the belief of obstetricians that the toxemia of pregnancy is especially dangerous to the future health of the patient. It is a curious and interesting fact that pregnant patients who have eclampsia and recover are left in better physical condition than are those who recover from toxemia without eclampsia. The excretory organs in eclamptic patients are in better condition than in those who do not have convulsions. Hence at the present time obstetricians are devoting their attention to the detection of toxemia in its early stages, with the hope of inducing labor sufficiently promptly to bring about a perfect recovery in the patient. With these facts in mind the importance of the writer's paper is evident. Space does not permit an extended review of this paper. The writer concludes that chemical study should in future be of definite value in averting the risk of permanent damage to the mother and indicating the stage at which the induction of labor becomes necessary. The definitely raised urea content of the blood above 40 mgm. per 100 cc is proof that the kidney is severely damaged and is an indication for induction of labor. Where the blood urea is not increased, the urea concentration test gives valuable evidence of the condition of the renal function, and when the figure obtained is below 2 per cent, termination of the pregnancy should be considered. It is of the utmost importance that both these examinations be repeated at regular intervals, the frequency depending upon the urgency of the case. If a rising blood urea is present with a falling concentration capacity, this is an obvious indication of a progressive lesion. Where the diastolic blood pressure is low, it is probable that there is chronic disease, and that a less complete recovery must be expected. Blood-pressure observations are valuable in all cases. We have no efficient and reliable method of estimating hepatic function. By the methods just described we can arrive at definite criteria for interrupting pregnancy.

**A Sign of Intrauterine Death.**—SPALDING (*Surg., Gynec., and Obst.*, June, 1922, p. 754) calls attention to the value of roentgen-ray pictures where during pregnancy there is fear of intrantrine fetal death. For a basis of study 27 patients in normal pregnancy were examined by the roentgen-ray. The outline of the fetal skull was distinct in each case; there was no overlapping of the bones, nor did there seem to be any shrinkage from a normal size. One patient who had a normal pregnancy had rupture of the membranes in the beginning of labor; she had a long first stage (forty-three hours) because of rigidity of the cervix, but she was

finally delivered of a living child. A roentgen-ray picture taken late in the first stage of labor showed marked overlapping of the fetal bone but no sign of diminution in the contents of the skull. The absence of diminution in the contents of the cranium showed that the condition was the result of pressure and not of fetal death. In three cases of intra-uterine death the roentgen-ray picture showed marked overlapping of the skull bones with distinct signs of shrinkage in the contents of the skull.

---

**Labor Complicated by Infected Fibroid.**—HOLLAND (*Jour., of Obst. British Empire*, 1922, 29,) describes the case of a multipara, aged thirty-five, who had been delivered three weeks previously, her child weighing six and a half pounds, and living but one day. The uterus remained large, the placenta did not come away and it was thought that a second child was present. At the end of three days, as nothing had happened, the attending physician removed the placenta by the hand and then made the diagnosis of uterine fibroid. A violent septic infection developed, and when the patient was brought to the hospital she had signs and symptoms of general peritonitis. The uterus was at once removed by supravaginal hysterectomy. On the anterior surface of the tumor there were two perforations, from which pus was oozing. The patient died thirty-six hours after operation. On examining the specimen the muscular capsule of the tumor was very thin. The perforations had occurred through this muscular capsule, and underneath the fibroid was sloughy and yellow in color. These perforations permitted the infective discharge from the uterus to gain access to the peritoneal cavity and set up peritonitis.

---

**Induction of Labor with Castor Oil and Quinine.**—WILLIAMSON (*Surg., Gynec., and Obst.*, June, 1922, p. 812) gives his results in induction of labor by the use of castor-oil and quinine in 300 cases. His study was suggested by two cases where these substances produced abortion. One was a primipara three months pregnant, who in six hours took 60 grains of quinine sulphate. She had marked signs of the action of the quinine, and had great pain at the time of abortion, but seemed to have recovered from the drug by the third day. The second patient was a multipara four months pregnant, who took an ounce and a half of castor oil and four grains of quinine. She had sharp pain with profuse vaginal bleeding, which suggested a premature separation of the placenta. In the cases studied, the patient was given a light dinner and in primiparae castor oil was given at midnight, in multipara at six or seven in the morning. One ounce and a half of castor oil was administered with orange juice or some other vehicle. So soon as the oil was effective an enema at 106°F. was administered, and immediately after this 5 grains of quinine was given and repeated at thirty-minute intervals until 20 grains had been taken. If the patient complained of ringing in the ears or nausea the quinine was stopped. The administration of a grain of pepsin with the quinine prevented nausea. Occasionally two doses of 10 grains were given two hours apart. The aid seemed to play no part in the occurrence of labor. If the attempt failed, the second trial was not made until ten days later. Of the 300 cases the method was successful in 140, unsuccessful in 160. In those where labor did not come on, all the primiparae were at full term except

20, and the head of the fetus had engaged in all but 8. The reason for attempting induction was moderately contracted pelvis or an impending toxemia. All the multiparæ were due at date excepting 28. In 20 of these patients the head had not engaged; induction was attempted because of toxemia or because the patient was going over time. The writer believes that this method is successful in about half of the cases. With these patients labor should be carefully watched, for occasionally the uterus contracts violently. If mother or child seems to be in distress the obstetrician should interfere at once. Quinine should be stopped as soon as there is evidence of cinchonism. This method is apt to be most successful when the patient is at full term or a little past, when the head is engaged in the pelvic brim and when the uterus is irritable. The mechanism of labor induced in this manner results from irritation by the castor oil on the sympathetic centers with increased peristalsis; and increase of the rhythm and muscle tone produced by the quinine acting directly on the uterine muscle.

---

**Rupture of the Uterus through a Cesarean Scar.**—GRAHAM (*Jour. Obst., British Empire*, 1922 29,) reports the case of an elderly primipara on whom he had performed a Cesarean section. A little more than a year later a pregnancy occurred and the induction of premature labor was attempted by the insertion of bougies. The pelvic contraction was not excessive, and it was hoped that vaginal delivery could be effected. As pains had not developed this treatment was abandoned, a Cesarean section performed, securing a living child. On this occasion the uterus was closed by two layers of continuous iodine-catgut sutures, and uninterrupted recovery followed. Two years later another pregnancy occurred and the advice was given to have Cesarean section with sterilization of the patient, as her general health was not good. Six weeks before term the patient was brought to hospital because of severe abdominal pain and profuse bleeding from the vagina. No fetal heart sounds were heard, but the child was unusually mobile. On opening the abdomen the uterus was found ruptured with the fetus and placenta free in the abdominal cavity. The patient recovered with hysterectomy. On examining the muscle of the uterus there was a general fibrosis. At the site of the last incision healing had been imperfect in the deeper two-thirds of the scar. The granulation tissue was cellular, vascular, and imperfectly organized. The epithelium of the endometrium had grown into the scar, showing that union had never occurred in the deeper tissues.

---

**Twin Pregnancy and the Diagnosis of Superfetation.**—CALDERINI (*Annali di Ostetricia*, January, 1922, p. 1) has studied a case of twin pregnancy and the possibility of diagnosing superfetation. He investigated the centers of ossification and also the placenta, which was one large placenta with two cords, and the two amniotic sacs divided by a partition. The paper has several good illustrations, showing the structure of the placenta and roentgen-ray examination of the skeleton. He finds that a positive statement regarding superfetation is difficult to make. All of the factors in the case must be thoroughly studied, and he believes that all data should be collected by clinics, so that they can be compared in the reporting of various cases. Evidently

greater study is required in the physiology of fecundation, before a positive diagnosis of superfétation can be made. (In this connection the reader's attention may be called to a recent paper by RADASCH, *Surg., Gynec. and Obst.*, April 1, 1921, p. 339.)

**Blood-pressure in Pregnancy.**—Normal blood-pressure of pregnant women has been studied by LITZENBURG, (*International Clinics*, 1921, 4). His series of cases numbered 524. Illustrative cases are cited, and the writer concludes that the normal systolic blood-pressure in pregnant women is from 100 to 130 mm., and not from 100 to 150 mm. as quoted by various writers. The normal diastolic pressure is from 60 to 85; and the normal pulse pressure from 30 to 50. Pressure above these averages indicates a pathological condition and demands close observation of the patient. In 30 per cent of these cases there was an increase of blood-pressure during pregnancy, and in 21 per cent a decrease; while low blood-pressure does not indicate that shock is inevitable, it points to a depressed condition of the woman's general health. One pregnant woman in ten had a systolic pressure above 130 and required special attention. In studying the toxemia of pregnancy an increase in blood-pressure is our most valuable sign. Albuminuria is also of great importance, but a high blood-pressure is present earlier than albuminuria. Where the tension increases, it forms a system of great value. All pregnant women whose systolic blood-pressure was above 180 were found to be definitely toxemic. When blood-pressure was above 160, 50 per cent were markedly toxemic; and when between 150 and 160, 35 per cent; when between 130 and 140, 3.5 per cent of patients were markedly toxemic. Other diseases than toxemia and some unknown conditions may cause high tension. The danger of convulsions increases steadily with systolic tension above 160 mm.; convulsions, however, may occur with moderate or low blood-pressure. Eclampsia in most cases can be prevented if pregnant patients are early and frequently examined, and in this examination the study of blood-pressure is of very great importance. This and the examination of the urine is our surest method of diagnosing toxemia.

## GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY  
OF PENNSYLVANIA, PHILADELPHIA.

**Elephantiasis Vulvæ.**—In discoursing upon elephantiasis of the vulva, or, as he prefers to call it, the hypertrophic-ulcerative form of



chronic vulvitis, TAUSSIG (*Amer. Jour. Obst. and Gynec.*, 1922, 3, 281) states that he believes that there is a distinct racial predisposition to this disease. When we consider that the negro makes up but one-tenth of the population of this country, it is striking that practically all of the cases of vulvar hypertrophy in the American literature are found among colored women. It is probable that this tendency to fibrous hypertrophies of the vulva among colored women has some relationship to the similar tendency to keloids and uterine fibroids in this race. Another factor to be considered in this disease is that the anatomic distribution of the lymph-channels of the vulva predispose to lymph stasis. In filarial infections the occurrence of a lymphatic enlargement in the inguinal and femoral region not only blocks the flow to the leg but also to the labium on the same side. Lymph stasis of some degree, whether in the groin or in the labia, must be considered as a *sine qua non* in the production of these enlargements. The looseness of the vulva skin makes possible the formation of chronic edematous deposits, with resulting fibrosis and enlargements of these parts. Together with the eyelids and the backs of the hands, the vulva is one of the first points at which a tendency to edema will be manifested. Uncleanliness is another important etiologic factor, as in no instance has this disease been found among women of the better classes. Persons with neglected syphilis and gross lesions about the external genitals may develop a slight thickening of the tissues, but if they are clean about their person they do not develop these extreme hypertrophic ulcerations. Often a syphilitic rectovaginal fistula, together with a gonorrhea, makes it difficult to keep the parts clean. On the other hand, once the condition has developed, the best care and hospital nursing, trying to keep the parts clean, will not materially influence the size of the mass or the extent of the ulcerations. The disease is found solely during the period of greatest sexual activity, and it is certain that the repeated traumatism of coitus, especially in prostitutes, has much to do with the production of hypertrophy. The frequent occurrence of tertiary syphilitic ulceration about the vestibular ring results in repeated injuries with resulting wound infection following coitus. The poor nutrition of these parts produced by the lymph stasis and obliterative endarteritis make wound healing slow, so that in most instances these ulcers do not heal entirely and must be excised. As to the nature of the infecting agent in this disease, there is much difference of opinion. Syphilis is found in from 80 to 90 per cent of the patients, but there is some difference of opinion as to whether the lesion is to be classified as a tertiary gummatous deposit or as a postsyphilitic process, since many of these cases have a negative Wassermann reaction with positive evidence of a previous syphilis. While text-books on gynecology have in the past emphasized filariasis as a factor, it is apparently rather rare. Tuberculosis of the vulva has been found in some few cases associated with these hypertrophic tumors. Gonorrhea is probably never a primary factor, but will often greatly increase vulvar irritation and so, secondarily, aids in the growth of the vulvar enlargements. Symptoms are usually insignificant in this disease, which may be due to the low state of intelligence and lowered pain sense in these individuals. Some discomfort from the weight of the pendulous mass, interference with

walking, and urinary and rectal irritability may be noted. A word may be added regarding the treatment of these cases. Antisyphilitic treatment, even the most persistent and vigorous, will not cure these cases and will only rarely and temporarily affect the size of the tumor mass. It is well, however, that such treatment be employed to promote prompt healing after surgical intervention. The record of the seven cases that underwent operation in Taussig's series shows the uniformly satisfactory results of vulvectomy in these cases, provided only that the incision be wide enough to include all indurated and ulcerated tissue and it is usually better to make this incision with the cautery.

---

**Action of Emetin Hydrochloride upon the Uterus.**—In Central Africa a few years ago MARTIN (*Amer. Jour. Obst. and Gynec.*, 1922, 3, 241) treated a white woman, in the sixth month of pregnancy, suffering from a dysenteriform enteritis (without amebæ in the stools). Not responding to ordinary treatment, she was given for three consecutive days one hypodermic injection of one grain of emetin hydrochloride. The drug had no action upon the enteritis and on the morning following the last injection the patient went into labor and aborted the same evening. This suggested to Martin to test the action of this drug upon the uterus, which he did by means of experiments upon laboratory animals. The most important finding in this work was that the action of emetin upon the uterus differed *in vitro* and *in vivo*. *In vitro* emetin lessens the activity of pregnant and nonpregnant uterus (dogs, rats, rabbits). It causes a decrease in tone and amplitude, although increasing the rate of contractions. *In vivo* emetin causes an increase in the tone of the uterus, both pregnant and nonpregnant (dogs and rabbits). Therefore it might be tested with caution in the treatment of metrorrhagia and menorrhagia, owing to the fact that it increases the tone of the uterus *in vivo*.

---

**Radium Treatment of Benign Bleeding.**—In presenting his opinions concerning the use of radium in hemorrhage from the uterus of benign origin, POLAK (*Med. Rec.*, 1922, 101, 493) first considers myopathic hemorrhages in young girls, which are frequently excessive, although they sometimes yield to the internal administration of endoerines and regulation of the lower bowel. When the bleeding has continued for any length of time the endometrium becomes hypertrophied, the uterus large and soft and the os is very likely to be open. These cases were formerly curetted after all other forms of internal medication had failed and a secondary anemia had been induced. After curetting there was usually an amenorrhea for a month or two, when this was followed by a metrorrhagia. This same case treated by radium for from 300 to 600 mgm. hours, with the radium properly filtered, will establish a normal menstruation after one seance. He has treated 31 such cases and in only 1 case was it necessary to repeat the exposure. Six of these girls are now married and two have become pregnant, a fact which answers some of the criticisms which are made of using radium in young girls. In regard to myomata, radium will control the hemorrhage from uterine myomata and in a large number of cases will reduce the size of the tumor, provided the tumor is intramural or submucous

and not pedunculated. Nevertheless operation is still the procedure of choice in most myomata, for the indications for radium are limited and it has certain definite disadvantages, such as: First, while it controls bleeding and the majority of cases show a reduction in the size of the tumor, nodules outside of the uterus may be left without a blood supply and consequently are more likely to give trouble. Second, malignant complications already in the tumor may be overlooked, for it has been shown that sarcoma is found in serial sections in about 9 per cent in submucous tumors; consequently we can lay down the dictum that radium is never permissible in submucous growths or unless a diagnostic curettage is possible, for while remarkable results have been shown following radiation of cervical cancer, body carcinoma is not amenable to the effects of the rays. Third, about 54 per cent of all fibroids are complicated by some form of tubo-ovarian disease; consequently many of these intrapelvic complicating lesions are missed, and while the tumor is shrunk and the hemorrhage controlled the associated lesions help to keep up the patient's invalidism. Fourth, radiation, when applied in sufficient dosage to check hemorrhage and shrink the tumor, will seriously impair the reproductive functions in young women, and therefore should not be used as a procedure of choice in this class of cases. Fifth, one of the symptoms of fibroids which requires treatment is the pressure symptom; here the effect of radium is too slow to relieve the condition which intraligamentous growths produce on the ureters and bloodvessels. Sixth, the immediate effect of radium is the production of edema and excitation of inflammatory reactions; hence, in the presence of old inflammatory adnexal lesions, this reaction becomes more marked. Finally, radiation will increase the necrosis in tumors which are already necrotic, and by added acidosis increase the toxemia of the patient. Against these disadvantages radium has certain definite advantages in treatment of fibroid tumors, particularly if the proper selection is made. These advantages are: First, there is no operative mortality, there is no general anesthetic, there are no postoperative complications, and there is prompt control of uterine hemorrhage. Second, should radium fail, operation is always possible. Third, the menopausal symptoms are not so marked. Fourth, in intramural tumors we cannot only expect absolute cessation of the hemorrhage, but shrinking in the tumor in over 65 per cent of the growths. Fifth, radium is the procedure of choice in myomata complicated by heart disease, extreme anemia, diabetes, and chronic nephritis. Of the 106 growths which Polak has radiated only 2 have needed subsequent operation. In 80 of the tumors the growth shrunk to less than half of the original size and in 20 cases it has entirely disappeared.

## PATHOLOGY AND BACTERIOLOGY

---

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

---

**The Action of Neoarsphenamine and Neosalvarsan on the Phagocytic Activity of Leukocytes.**—To test the action of arsenical compounds on phagocytosis, TUNNICLIFF (*Jour. Infect. Dis.*, 1922, 30, 545) mixed equal parts of neoarsphenamine in salt solution, normal human serum, suspensions of washed human leukocytes and of strains of *Streptococcus viridans* not spontaneously phagocytizable which were incubated for twenty-five minutes. Salt solution alone was used in the controls. The mixtures were smeared on slides, stained with carbol thionin and at least 100 polymorphonuclear leukocytes were counted. To determine whether the effects on the degree of phagocytosis were on the leukocytes themselves, equal numbers of washed leukocytes were suspended in different dilutions of the arsenical compound for one hour at room temperature. The leukocytes were washed twice in salt solution and equal quantities of serum and bacteria added, incubated for twenty-five minutes and smears made as before. It was found that solutions of neoarsphenamine below 1 to 1000 stopped or greatly reduced phagocytosis, while dilutions between 1 to 10,000 and 1 to 100,000 increased phagocytosis on an average more than twice. Five of seven rabbits each injected with 0.007 gm. of neoarsphenamine showed a decided increase in the number of leukocytes in from fifteen to thirty minutes following the administration and the leukocytes were from 2 to 6 times more actively phagocytic than normal at fifteen minutes after inoculation of the arsenic compound. No changes in the opsonic index were observed. Two patients showed no leukocytosis after injection, but in thirty minutes subsequent to inoculation there was an increased phagocytic activity of the leukocytes. This activity disappeared fifteen minutes later. Similar results were obtained with neosalvarsan. For reasons stated in the context, the author believes that the arsenic compounds were directly responsible for the increased phagocytic activity.

---

**Studies on the Nature of the Action of Nonspecific Protein in Disease Processes. III. Nonspecific Proteins and Soluble Toxin.**—Having demonstrated before that 1 cc of normal horse serum when injected subcutaneously into guinea-pigs will protect against a fatal dose of diphtheria toxin and may protect against as high as eight fatal doses and that the protein of normal horse serum (precipitated by alcohol) will also protect against diphtheria toxin, COWIE and GREENHALGH (*Jour. Med. Research*, 1922, 43, 21) continued their experiments

to ascertain whether this protecting action is due to the protein or to native antitoxin. It was learned that the protective action of normal horse serum precipitated by alcohol is much less than that of untreated horse serum; that the globulin (alcohol treated) fraction of horse serum protein is more effective than the albumin fraction similarly treated; that the nonalcohol treated globulin fraction of 1 cc of normal horse serum will protect against several fatal doses of diphtheria antitoxin, while the alcohol-free albumin fraction furnishes no protection; that no protective action against diphtheria toxin was observed when egg white, milk and guinea-pig and rabbit serum were used, and that 1 cc of normal horse serum when injected subcutaneously into a guinea-pig will protect against a fatal dose of tetanus toxin. From this evidence the authors believe that the protective action of normal horse serum against soluble toxin is due to natural antitoxin in the serum and not to the effect of the nonspecific protein.

---

**An Experimental Study of the Effects of Protein Injections upon Infections.**—In view of the results which have been reported relative to the favorable influence of protein injections upon various infections and the practical absence of unfavorable comment, KROSS (*Jour. Med. Research*, 1922, 43, 29) conducted three series of experiments in order to test the effect of protein therapy upon certain infective processes in animals. Accordingly, white rats were inoculated with mouse typhoid bacilli, a general peritonitis was produced in rats, rabbits and guinea-pigs by soiling the peritoneum with their own gastric or intestinal contents and rabbits were injected intratracheally with a virulent broth culture of *Pneumococcus* I. The protein was administered by subcutaneous, intraperitoneal and intracardial methods in different groups and consisted of 1 cc of a 1 per cent solution of nucleinic acid. It was found that the protein did not increase the resistance of the animals to any of the infections experimentally produced. The treated animals could not overcome the infection any better than the untreated ones. Moreover, the protein inoculation seemed to reduce the vitality of the animals and the danger of death from anaphylactic shock was "such as to stamp this method of treatment as actually threatening great potential harm."

---

**Frequency of *Bacillus Influenza* in the Nose and Throat in Acute Lobar Pneumonia.**—STILLMAN (*Jour. Exper. Med.*, 1922, 35, 7) reports the incidence of *Bacillus influenzae* and *pneumococcus* in the noses and throats of patients with acute lobar pneumonia and refers to the frequency of the former organism in cultures recovered from normal individuals. The throat cultures were obtained by passing cotton swabs over the posterior pharyngeal wall and the nasal cultures by passing cotton swabs through a sterile speculum into the nares. The swabs were inoculated on freshly poured oleate hemoglobin plates and on fresh blood-agar plates. In 31 cases of pneumonia 18 (58 per cent) showed influenza bacilli in the throat and from 35 pneumonia patients, the same organism was isolated from the nose on 9 occasions (23 per cent). In certain other cases, influenza bacilli were encountered in the sputum when they were not found in the nasal or pharyngeal cultures, so that among the entire 35 cases, influenza bacilli were isolated from at

least one of these three sources in 30 or 85 per cent of cases. Of 1077 normal individuals *Bacillus influenzae* was found in the throats in 30 per cent. Whereas pneumococci were rarely encountered in the nose cultures of normal persons, they were demonstrated in 15 of the 35 cases of lobar pneumonia, the majority of which were found to be the same type as the organisms in the lung lesions as shown by sputum determination. The influenza bacilli encountered in this work were of various types. The author states that the exact significance of these findings is at the present time not clear.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

**Carbon Tetrachloride: A Drug Proposed for the Removal of Hookworms, With Special Reference to its Toxicity for Monkeys when Given by Stomach Tube in Repeated Doses.**—LAKE (*Public Health Reports*, 1922, 37, 1123) reports on experiments on monkeys designed to determine the effect of carbon tetrachloride which is coming into use as a treatment for hookworm infestation. The results are summarized as follows: (1) Four monkeys received carbon tetrachloride by stomach tube in amounts of 1, 2, 3, and 5 cc respectively, at intervals of two to three days, over a period of from thirty to forty-one days, the total number of doses varying from 12 to 16. (2) No symptoms of importance were shown by the monkeys during this period. (3) The two monkeys receiving the larger doses were subsequently used for the testing of suspected poliomyelitis virus and died of brain abscess. In each case gross and microscopic examination of the important organs failed to show any changes indicative of an exogenous poisoning. (4) The doses received by the monkeys at each treatment were from 10 to 40 times greater in cubic centimeters per kilogram of body weight than the dose mentioned by Hall as that indicated for man, and these doses were repeated from 12 to 16 times. From the data at hand we must conclude that carbon tetrachloride by stomach has a very low toxicity for monkeys and that it is probable that man may safely be given considerably higher doses than the ones suggested by Hall, and that it might be safe to repeat the dosage several times at proper intervals (one week). Finally, in view of the unusually promising results that carbon tetrachloride has given as an anthelmintic for hookworms in

animals, and in view of its unusually low toxicity for animals, including monkeys, when given by stomach, both in single and in repeated doses, we believe that it deserves an extensive trial in the treatment of hook-worm diseases in man.

---

**A Rapid Method of Determining the Presence and Type of Botulinus Toxin in Contaminated Foods.**—Realizing the importance of an early diagnosis of botulism, ORR (*Jour. Infect. Dis.*, 1921, 29, 287) has utilized white mice, some of which have been injected previously with Type A antitoxin and some with Type B antitoxin in arriving at the knowledge of both the presence and type of botulinus toxin in contaminated foods. About 0.5 cc of the filtrate of the infected food was introduced intraperitoneally into normal mice and mice protected by the Types A and B antitoxin. If previously immunized mice are not available, it is efficient to mix some of the suspected toxic filtrate with Type A antitoxin and some with Type B antitoxin and then inject the mixture into mice. As the specificity of the toxin and antitoxin of the two types, A and B, is very distinct, if the food contains the toxin of *Bacillus botulinus* A, the mice receiving no antitoxin and those receiving Type B antitoxin will die, while those receiving Type A antitoxin will survive. On the other hand, if the food contains toxin of the Type B organism, only those receiving Type B antiserum will live. In this way both the presence and the type of toxin may be determined in from four to six hours. As the toxin may be present in weak concentration, it is advisable to inoculate some mice with larger quantities of the suspected filtrate.

---

**Smallpox in Twenty States.**—FORCE and LEAKE (*Public Health Reports*, 1921, 36, 1979) make an analysis of state laws and regulations bearing on smallpox vaccination, and compare the results with the rates in the states under consideration. Their conclusions are as follows: "From a study of these statistics and procedures it is evident that smallpox in this country is dependent on the popular vote. In general the people obey laws which they have made. If popular sentiment in a state is behind a strong centralized compulsory vaccination act, smallpox is negligible in that state. If local authorities are given discretionary powers in the matter of vaccination enforcement the rate tends to rise, even in the most favored sections of the country, whereas in the absence of compulsory features of the law, or where there is no law at all, smallpox reaches a high rate."

---

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL*.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript*.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

NOVEMBER, 1922

---

ORIGINAL ARTICLES.

ENDOCRINOLOGY AS A KEY TO THE SOLUTION OF  
MAJOR MEDICAL PROBLEMS.\*

BY CHARLES E. DE M. SAJOUS, M.D.,

PROFESSOR OF APPLIED ENDOCRINOLOGY, UNIVERSITY OF PENNSYLVANIA  
GRADUATE MEDICAL SCHOOL.

THE opening scientific address of a new society should logically embody a review of the actual status of the field to which its labors are to be dedicated. In the present instance this custom assumes almost the importance of a duty, in view of the fact that at no time in its history has endocrinology, with the exception of the diseases of the ductless glands themselves, stood in a more precarious condition than it does today, particularly in this country. The physiologists, as will be shown presently, having failed to discover the functions of these organs notwithstanding painstaking efforts to do so, have left the endocrinologic ship, as it were, without a rudder, in so far as the clinician is concerned, as a guide for sound investigation, particularly in pathogenesis and therapeutics. The inevitable result, which I tried to forestall many years ago, has been to divide the profession at large into two camps: The ultraconservatives who are, with just cause, frightened off by the maze of groundless and unsupported theories with which the whole subject has been surrounded in recent years, and the overconfident who are the authors of the unwarranted theories and who administer organic products in practically all disorders without regard for physiologic effects. Even this overenthusiasm is to

\* Read by invitation at the first scientific session of the Endocrinological Society of the city of New York, January 6, 1922, and before the Mercer County Component Society, Trenton, N. J., February 8, 1922.



be attributed, however, to the absence of knowledge concerning the role of the organs themselves in the body. Indeed, five years ago Prof. W. S. Halsted, of Johns Hopkins, after a serious effort to elucidate an endocrine problem, was finally led to conclude that "it must be evident to everyone that there reigns the greatest confusion on the subject of the functions of the glands of internal secretion." Today he might say with equal justice that this applies as well to the whole domain of endocrinology as it is generally interpreted, and that the confusion is steadily growing apace with time.

Might there not exist an intermediate class of clinicians who practice what might be termed scientific endocrinology? That there exists such a group it is my privilege to assert. After reviewing in greater detail the underlying cause of the prevailing confusion, the absence of adequate physiologic information, I will submit the reasons which led to the elaboration of this higher aspect of endocrinology and, by a few examples, briefly portray what it would mean to medical progress if its teachings were generally adopted in lieu of the present chaos to which the term "endocrinology" is attributed.

**The Physiology of the Endocrines as Interpreted by Physiologists Affords no Aid to the Clinician.** In making this statement, assurance may be given that there can be no question on my part of antagonism to physiology. Indeed, for the last forty years, first as professor of physiology in the Wagner Institute of Science in the early eighties, as editor of the *Annual of the Universal Medical Sciences*, in which Prof. Newell Martin and Howell, of Johns Hopkins, were my valued collaborators, and recently in the presidential address before the Association for the Study of the Internal Secretions,<sup>1</sup> I earnestly urged the importance of coöperative harmony between physiology and clinical medicine as a *sine qua non* of medical progress. It is the lack of this feature which, as we shall see, has prevented to this day the discovery by physiologists of the functions of any ductless gland, without a knowledge of which the clinician—meaning thereby the physician, the pathologist, the surgeon, the specialist, etc.—cannot work out his own problems. His normal source of information, in view of his own arduous occupations, is the text-book of physiology. What does he find even in the best of these works?

Beginning with the adrenals the truth soon asserts itself. Despite the pioneer labors of Brown-Séquard in 1856; despite the convincing researches of Oliver and Schäfer upon their cardiovascular tone theory, of Abelous and Langlois upon their antitoxic theory, of Cannon upon his emergency theory and others—all have virtually been swept by the wayside. If the clinician tries to solve for himself the problem in question with the aid of physiologic literature he soon finds himself in a maze of contradictions con-

tributed by undoubtedly able men, but which, nevertheless, leave as leading impression a suggestive unreliability of their work. And yet a few physiologists, Stewart<sup>2</sup> and Gley<sup>3</sup> and their followers, overlooking the fact that experiments in *normal* animals can only, from the standpoint of exact science, portray the effects of precisely similar experiments in *normal* men—since any degree of pathology, a toxemia, the defensive process, organic lesions, etc., modifies the whole picture—have recently published interpretations of some clinical aspects of endocrinology, notably adrenal insufficiency, which close scrutiny and clinical experience fail totally to sustain. Nor can it be otherwise in the absence of any foundation for their argument. Indeed, physiologic knowledge on this score was frankly expressed by Swale Vincent,<sup>4</sup> now professor of physiology in London University, when he wrote, "We know nothing of the adrenal body on its own account."

The situation concerning the thyroid is quite as unsatisfactory. Notwithstanding the labors of Schiff, begun in 1856, which soon followed those of Reverdin and Kocher in the clinical field, and the later investigations of Horsley, Jeandelize and others, all affording ample proof of the influence of this organ upon nutrition and metabolism, Prof. Howell,<sup>5</sup> of Johns Hopkins, states in the last edition of his text-book of physiology that "no explanation has been furnished in respect to nutrition"; and that "the details of its influence on metabolic processes are for the most part unknown." Hence the fact that confusion also reigns in the clinical field. Since Kendall isolated the active principle thyroxin,<sup>6</sup> which profoundly accelerates metabolism, his (admittedly theoretical) view is that its function is "to furnish the animal organism with ammonia resulting from the deaminization of amino-acids." But it is at best difficult to reconcile this process with the increased intake of oxygen, following the feeding of thyroid, which varies from 20 to 75 per cent in myxedema and 10 to 40 per cent in animals, and the corresponding output of carbon dioxide. Nor does it explain the increased elimination of phosphoric acid observed by Chittenden and others or the familiar rapid reduction of fat which thyroid preparations provoke. While Kendall's conception may be sound, the manner in which the thyroid hormone influences nutrition and metabolism remains as obscure as it has ever been.

The physiologic functions of the parathyroids are no more lucid. The etiologic connection between removal of these organs and fatal tetany, first pointed out by Gley, has been shown to apply to carnivorous and about one-half of herbivorous animals. But how the parathyroids carry on the surmised process of breaking down the spasmogenic wastes is admittedly unknown. As Prof. Brubaker,<sup>7</sup> of Jefferson College, states, "It is evident that the subject needs further investigation."

The thymus also belongs to the "obscure" series, the more recent

experimental labors having virtually eliminated all importance to the functions formerly attributed to them. Howell<sup>8</sup> states in this connection that "the physiology of the thymus is very obscure; in fact, nothing that is definite can be said about its functions, except perhaps that the gland is concerned in some way with the processes of growth."

The pineal is no better off. After summarizing the investigations upon this organ, Prof. Schäfer,<sup>9</sup> of Edinburgh University, concludes with the statement, "It must be admitted that the results of clinical observations and experimental work in animals are at present difficult to reconcile and do not enable us to come to any definite conclusion regarding the functions of this organ and the nature and mode of action of its autocoids."

Concerning the pancreas, its internal secretion is now recognized as separate from that poured into the intestines. About all that may be considered established, however, even though pathologists have contributed much to the subject, is that the islets of Langerhans carry on some specific function—probably in sugar metabolism. Howell states that "the nature of this function and its relation to that of the acinar glands must be considered at present as open questions."

The functions of the pituitary body are equally obscure. Acromegaly is attributed to excessive secretory activity of the anterior lobe, but ample experience has shown that extracts of this lobe, even in enormous doses, or Robertson's tethelin, fail to cause growth in human beings or anything suggesting acromegaly. Again, the posterior pituitary, the source of the very efficient hypophysis sicca, pituitrin, etc., is supposed to represent a secretion. But, as Prof. Swale Vincent,<sup>10</sup> of London (and also Biedl), in keeping with my own previously published views, says of this lobe, "It is extremely difficult to imagine how such a structure can be regarded as a secreting gland." The same physiologist also states, "We know, after all, very little about the normal functions of the pituitary—no more, in fact, than we know about those of *any other of the ductless glands.*"\*

Such disappointing results would seem to be offset by the discovery of the endocrine active principles, some of which, at least, are serving so useful a purpose in every branch of practice. But, in truth, credit for them does not belong to physiologists. Abel, who gave us epinephrin, is a pharmacologist. Takamine and Aldrich, who discovered adrenalin, are chemists associated with manufacturing pharmacists. Kendall, who isolated thyroxin, and Robertson, who isolated tethelin, are both chemists.

The endocrines reviewed suffice to illustrate the inability of physiology alone, even as interpreted by its masters, to aid the

\* All italics are my own.

clinician interested in the endocrinologic field. Any unbiased observer would conclude, in fact, that labors which had given such a paucity of results after researches covering the whole period elapsed since Claude Bernard introduced the term *sécrétion interne*, over sixty years ago, should be relegated to the long list of abortive efforts.

And yet would any degree of exclusion of physiologic labors be justified by facts? No greater calamity could befall endocrinology than such a course. During the period mentioned physiologists have accumulated a vast store of sound physiologic data which are invaluable in the development of this new branch of science, but their true worth is only brought to light, we shall see, through harmonious coöperation with other branches of medical knowledge, including, particularly, clinical medicine and pathology.

**The Coöperation of Various Medical Sciences Necessary to Ascertain Endocrine Functions.** Although it was Brown-Séquard, a physiologist, who gave the first impulse in 1856 which started modern endocrinology on its active career, the internist, realizing fully that to each quadruped, dog, cat, guinea-pig, frog, etc., studied by physiologists, he, as practitioner, pathologist, histologist, etc., studied hundreds of bipeds, men, women and children, soon learned from experience what a great physiologist, Pawlow,<sup>11</sup> emphasized twenty years ago, referring to the discovery, by clinicians, of the gastric secretory nerves, when he wrote: "Physiologists, on the other hand, had *fruitlessly endeavored for decades\** to arrive at definite results upon this question. This is a striking but by no means isolated instance where the physician gives a more certain verdict concerning physiologic processes than the physiologist himself; nor is it indeed strange. The world of pathologic phenomena is nothing but an endless series of the most different and unusual combinations of physiologic occurrences which *never make their appearance* in the *normal* course of life. It is a series of physiologic experiments which Nature and life institute, often with such an interlinking of events as could never enter the mind of the present-day physiologist and which *could scarcely be called into existence by means of the technical resources at our command*. Clinical observation will consequently always remain a rich mine of physiologic facts."

In the field of endocrinology clinicians also found that physiologists had "fruitlessly endeavored for decades" to create a solid foundation for functional phenomena so obviously merged with morbid manifestations observed on all sides. They reverted, therefore, to the labors of men in their own field as starting-points of their own investigations: Addison (1849) for the adrenals;

\* All italics are my own.

Reverdin (1882), Kocher (1883), Möbius (1886) and Murray (1891) for the thyroid; Pineles (1904) and MacCallum (1912) for the parathyroids; Paltauf (1891) and Bourneville (1900) for the thymus; Langerhans (1869), Laguesse (1893), Minkowsky and Mehling (1898), Lépine (1898) and Opie (1900) for the pancreas; Pierre Marie (1886), Launois and Roy, Fröhlich and Cushing for the pituitary, and many others, all of whom initiated questions which the labors of a multitude of investigators, both in the clinic and in the clinical laboratory, have served to bring to fruition as well-grounded endocrinologic entities. Hence the splendid results attained in our knowledge of the diseases of the endocrines *per se* and in their successful treatment, medical and surgical. It is not here that chaos reigns, however, but in the bearing of the endocrines upon general diseases and their treatment—precisely where the crying need for elucidation is greatest and where death still stalks unhampered in many directions.

Over three decades ago I realized as editor of the *Annual of the Universal Medical Sciences* that medicine as a whole was sodden—as it is still—with discrepancies and gaps which some general fundamental factor seemed alone capable of filling. While twelve years' (1880 to 1891) clinical work at Jefferson College Hospital (which included cases of goiter and exophthalmic goiter) had suggested the ductless glands as candidates for research, physiology proved of incalculable value in the independent analysis subsequently undertaken.

The effort made to fill at least some of the gaps found meant prolonged researches, both in the laboratory and in literature, utilizing, in so far as the latter was concerned, only data which had been confirmed, though giving also due consideration to those which seemed discordant. The method adopted was a novel one, in the sense that all subdivisions of science bearing directly or indirectly upon the solutions sought were utilized, all laboratory or clinical researches required and within my reach being carried out after the contributions of literature had been collected, coördinated, analyzed and then synthetized according to their mutual relationships. Thus data from zoölogy, histology, physiology, pathology, pharmacology, biologic chemistry, clinical medicine, surgery, etc., were used in the upbuilding of each subdivision of the subject studied, the postulate or conclusion reached representing, as it were, a mosaic of all knowledge available on the subject. Discordant data often proved not to be such, for if based on solid observation they usually found in the other branches of knowledge one or more links or connections which converted them into valuable assets. This plan not only avoided theorizing, since the conclusion reached was the end-product of a large number of data from varied sources, but it revealed also erroneous data owing to their inability to fit anywhere.

The conclusions reached and what data a book could accommodate were presented in my work on the *Internal Secretions and the Principles of Medicine*,\* the first volume of which appeared in 1903 and the second in 1907. It introduced what appeared to me, at least, a promising outlook for more rapid advance in medical knowledge, for the ductless glands, interpreted from my viewpoint, seemed to fill many of the discrepancies and gaps which both clinical medicine and therapeutics had shown. Swale Vincent clearly outlined the scope of the work when he wrote,<sup>12</sup> "Sajous apparently postulates a relationship between all the ductless glands, whose functions, according to this writer, dominate most of the bodily activities, normal and pathologic." It was, I might add, the first effort of its kind.

That the plan was a sound one is shown by the fact that although the physiologists have failed, during the nineteen years elapsed since it was carried out, to reveal, for instance, the functions of the adrenals—and this applies to other organs—the many data which their labors have accumulated upon this question, and which proved useless to them, have contributed all along to the support of my original conception of these functions. Among the cardinal functions which had remained *sub judice*, and which, from my viewpoint, this method has served to explain, is that of respiration. Its analysis will serve as an example of the value of the mode of research described in the study of obscure problems.

**Pulmonary and Tissue Respiration as an Endocrine Function.** The respiratory process as now taught in our schools, and despite its vast importance in all diseases, has been known to be defective for over sixty years (Vulpian,<sup>13</sup> Paul Bert,<sup>14</sup> Barnes,<sup>15</sup> Laulanié<sup>16</sup> and others). Briefly the prevailing diffusion theory was found unable to account for oxygen tensions in the arterial blood exceeding those in the air of the lungs; nor for the absorption by the venous blood of all oxygen in the pulmonary air in strangulated or asphyxiated animals; nor for respiration in the greatly reduced oxygen of high altitudes (Bohr,<sup>17</sup> Haldane and Lorrain Smith,<sup>18</sup> Harley<sup>19</sup> and Pembrey<sup>20</sup>). As Bohr pointed out in 1891, and other physiologists have since held, a substance having greater avidity than blood itself was necessary to explain the respiratory process.

In 1903 I submitted that the substance sought was the secretion of the adrenals. The work included besides the analysis of the literature of the subject, laboratory studies of the respiratory system in the lower forms, including insects, crustaceans, mollusks, fishes, batrachians, etc., ascending the phylogenetic scale to man, also of the biochemical reactions of fluids connected with the respiratory process; of the anatomic relations of the organs exposed to

\* These words are italicized to emphasize the purpose of the work from the start, i. e., the relationship between the endocrines and the practice of medicine proper.

oxygen-containing media; and finally clinical observations. All of these, including data from literature when coördinated and analyzed, pointed clearly to the adrenals, particularly in view of the marked reducing power of fresh adrenal extracts (Vulpian,<sup>21</sup> Cybulski,<sup>22</sup> Langlois<sup>23</sup> and others) as capable of carrying on the respiratory process.

Since then it may be said that every general feature of the respiratory process, as I interpreted it originally, both pulmonary and systemic, has been confirmed. Adrenalin has been found experimentally to facilitate the free circulation of air in the pulmonary air cells by causing dilatation of the bronchioles (Menten,<sup>24</sup> Jackson,<sup>25</sup> Dixon<sup>26</sup>). It is capable of converting venous blood into arterial blood on exposure to the air and of converting hemoglobin into oxyhemoglobin (Kariya and Tanaka,<sup>27</sup> Menten and Crile,<sup>28</sup> Menten<sup>29</sup>). It increases the intake of oxygen, the output of carbon dioxide, the volume of air breathed, the respiratory excursions of the lungs and the depth and rate of respiration (Byelaventz,<sup>30</sup> Bernstein and Falta,<sup>31</sup> Menten,<sup>32</sup> Tompkins, Sturgis and Wearn,<sup>33</sup> Sandiford,<sup>34</sup> Januschke and Pollak,<sup>35</sup> and Nice, Rock and Courtright<sup>36</sup>).

As regards its systemic effects, we have just seen that adrenalin can convert hemoglobin into oxyhemoglobin. In keeping with this observation adrenalin has been found in the blood and red corpuscles (Mulon,<sup>37</sup> Battelli<sup>38</sup>). It takes an active part in tissue oxidation; *i. e.*, cellular metabolism, as shown by many facts. Thus it raises the temperature even in small doses (Oliver and Schäfer,<sup>39</sup> Morel,<sup>40</sup> Lépine<sup>41</sup>) while accelerating metabolism (Reichert<sup>42</sup>). Large adrenal grafts also raise the temperature sufficiently, in some instances, irrespective of any infection, to have caused death (Courmont,<sup>43</sup> Bra<sup>44</sup> and Jaboulay<sup>45</sup>). Even malignant adrenal tumors, regardless of histologic structure, run a febrile course irrespective of any fever causing complication (Israel<sup>46</sup>). As small a dose as 0.5 cc. of adrenalin in 73 experiments in endocrine patients caused an increase in the basal metabolism rate (Sandiford<sup>47</sup>). It causes an increase in the intake of oxygen and in the output of carbon dioxide before accelerating the metabolic rate (Tompkins, Sturgis and Wearn<sup>48</sup>). Moreover, adrenalin in appropriate doses increases the excretion of urea (Addis, Barnett and Shevsky<sup>49</sup>).

As controlling evidence, removal of both adrenals should be followed by the opposite phenomena. Briefly it should reduce both the intake of oxygen and the output of carbon dioxide, cause dyspnea, lower the temperature and the metabolic rate, cause myasthenia through slowed muscular metabolism and relaxation of the cardiovascular musculature. That such is the case has been known ever since the time of Brown-Séquard. More precise methods being available the basal metabolism rate has been found

markedly lowered after the operation (Aub, Forman and Bright<sup>50</sup>) and the urea excretion likewise (Bovier and Shevsky.<sup>51</sup>)\*

If facts count at all these few data—which represent but a fraction of those collected and which cover but a small part of the process—should prove convincing in these days when experimentation, a single experiment sometimes, is thought to decide a question. They should mean much when, realizing that tissue oxidation takes part in every morbid process, general or local, we are brought face to face with Halliburton's statement,<sup>54</sup> which corresponds with others that could be quoted, in the last edition of his text-book of *Physiology*, "Our knowledge of tissue respiration is so scanty that we can say little about its pathologic bearing."

**The Endocrines in the Genesis of Fever.** Turning to the practical bearing of the function of tissue oxidation, as explained, we are brought to realize that the same obscurity reigns concerning its corollary, fever, notwithstanding its preponderating importance in disease. As stated by Lazarus Barlow<sup>55</sup> eighteen years ago, "Even if we grant that fever is beneficial we are completely ignorant of the manner in which it acts." Present-day text-books speak in the same vein. Analysis of the question, however, again confirms the correctness of the explanation of this process I submitted many years ago. MacCallum,<sup>56</sup> for instance, in his recent text-book refers to Rolly and Meltzer, Loewy and Richter, Fukahara and others as having found that if animals were kept at high temperature in a thermostat room they were able to develop a much more effective defence against intoxication and infection than those left outside at ordinary temperatures. If small doses of bacteria or toxin were injected at intervals, "The heated animals showed a great advantage over the controls. They lived longer and many of them survived doses which inevitably killed the control animals." Yet no explanation of the manner in which this phenomenon is produced is vouchsafed.

It may be accounted for, however, by the simultaneous action of several ductless glands. We have seen that adrenalin, when produced in excess, raises the temperature; but so does the thyroid secretion which also, as in fever, first breaks down fats. I submitted in 1903-1907 that both glands took part in the process, the thyroid hormone by increasing the lability of the phosphorus in all nuclei (which all contain organic iodine, as shown by Justus<sup>57</sup>) beginning with those of the fat cells, to the action of the oxygen carried to the tissues by the adrenalin-laden oxyhemoglobin, heat being liberated in the process. I urged also, as had Metchnikoff in respect to phagocytes, that the bacteriolytic and antitoxic pro-

\* Suggestive in this connection is the fact that while in 1903 German reviewers characterized tissue oxidation as the outstanding feature of my labors on the adrenals, Weil,<sup>52</sup> in his recent (1921) book on the endocrines concludes that these organs are directly concerned with oxidation.



cess in the plasma was due to a trypsinic enzyme which Abderhalden subsequently termed "defensive ferment," bacteria, toxins and other poisons susceptible to its action, being digested by them much as they were in the intestinal canal.\* As all biochemists know, however, digestive enzymes are active according to the temperature to which they are subjected, the laboratory maximum temperature of trypsin being about 104° F. This accounts for the fact that heat, whether endogenous, as produced by the interaction of thyroid, the adrenal hormone and the phosphorus of nuclei, nucleoli, etc., or exogenous, as developed in a thermostat, increases the efficiency of the body defences, the purpose of fever.

How is the process governed? MacCallum states in this connection, "As to the nature of the regulating centers nothing is known," but he also remarks, referring to a possible nervous control, "It appears that destruction or interruption of the hypothalamic region of the midbrain throws out of function the regulatory mechanism so that the warm-blooded animal becomes poikilothermic and makes no response to the usual causes of fever." Again has time sustained my personal views—reached by means of the analytic method described—submitted years ago,<sup>58</sup> which showed that while removal of the cerebrum from the midbrain did not prevent the genesis of fever or even the action of antipyretics, sufficient interruption of impulses through a nerve path leading from the pituitary to the thyroid and adrenals did so. Papers by Roussy and Camus, Houssay and others have more recently emphasized its presence by showing that tumors located in this region produced—doubtless by similarly blocking the path—evoked all the phenomena of pituitary insufficiency, polyuria, obesity, tardy development, etc. As illustrated in a colored plate forming the frontispiece of all ten editions of my treatise on the internal secretions, this path passes upward from the pituitary body to the tuber cinereum, thence along the basal tissues to the bulb and cord, and emerges to meet the thoracic sympathetic, the lowest branch entering this system, to pass below and enter the splanchnic nerve on its way to the adrenals—about the level of the third dorsal vertebra—a location recently confirmed by Stewart and Rogoff<sup>59</sup> by means of cross-sections of the spinal cord. On the whole it

\* As Mendel (Jour. Am. Med. Assn., March 24, 1906) states: "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism." This applies also to plant physiology, "all known proteolytic enzymes of plants," as stated by Vines (Ann. Botany, 1901, 15, 572), "being trypsinic." The main active bactericidal agent of phagocytes has been identified by Metchnikoff, Bordet and others as trypsin; this ferment has also been found to digest bacteria in the intestinal canal by Charrin and Levaditi, Zaremba and others. Vaughan also states that "the cell which can no longer supply a digestive ferment is already dead," while Opie clearly associates digestive ferments with the defensive functions of the body when he says that "the ability of the blood to remove injurious material is dependent on the possession of proteolytic enzymes."

would seem as if I had been justified in concluding many years ago that the regulating center of the febrile process was located in the pituitary body and that its influence on fever was exerted through a nerve path governing the functional activity of the thyroparathyroid apparatus\* and the adrenals.

All this exemplifies the beneficial side of the endocrine glands, the adrenal, thyroid and pancreatic internal secretions and the pituitary body (the latter only as a coördinating mechanism) coöperating in defending the body against disease.

**The Endocrines in the Genesis of Hyperthermia and Autolysis.** The prevailing obscurity concerning the nature of three kindred factors, tissue oxidation, fever and the role of the enzymes in the latter, is in my opinion responsible for a large proportion of untimely deaths. From the fact that the underlying cause of temperature production, oxidation, is unknown, it is obvious that the fluctuations of temperature, hypothermia and hyperthermia or pyrexia are likewise. In the light of the foregoing interpretations, however, these phenomena can be accounted for. Reserving hypothermia for the next section we will take up the effects of excessive temperature.

We have seen that adrenal grafts may raise the temperature to such a degree as to cause death irrespective of any infection. Hyperthyroidism may likewise cause a marked elevation of temperature, 110° F., for instance, as in a case observed by Rendu.<sup>62</sup> All clinicians know that danger threatens when 105° F. is exceeded. Below this limit, normal fever is the expression of active but safe defence; the trypsinic enzyme then limits its proteolytic action, both in the phagocytes and in the blood, to the pathogenic organisms, toxins, etc., present. When, however, this temperature is surpassed the structures in immediate contact with the blood or within it are first exposed to the digestive process of the "defensive" ferment, the red corpuscles yielding first (hemolysis), then the cardiovascular endothelium, the serous membranes, peritoneal, pleural, pericardial, meningeal, etc. (autolysis), according in a measure to the virulence of the pathogenic agent as an antigen and the local vascular supply.

Valvular lesions, for instance, are now attributed to the direct action of the pathogenic bacteria themselves, but this has never been demonstrated. If it were true, how account for their production by Christian and Walker<sup>63</sup> with uranium nitrate, potassium bichromate, arsenic in various forms, spartein and adrenalin

\* The protective influence of this apparatus against certain infections has been confirmed in various ways. Lévi and Rothschild<sup>60</sup> write in this connection: "Sajous has attributed among the functions of the thyroid body a role which he assimilates to that of opsonins and autoantitoxins. Fas-in, Stepanoff and Marbé have all confirmed the influence of the thyroid on the blood's action in alexins and opsonins." The two latter investigations were conducted at the Pasteur Institute of Paris. Col. McCarrison<sup>61</sup> also concluded after experiments that "the thyroid gland contributes largely to the body's antitoxic and bactericidal functions."

given in succession? All these drugs, as I have shown elsewhere,<sup>67</sup> are capable, either directly or indirectly, of enhancing the functional activity of the pancreas,\* and also by promoting a reaction of the adrenals and thyroid, thus accelerating tissue oxygenation and increasing the lability of the cellular nucleins, raise the proteolytic activity of the trypsin. The soundness of this conception is suggested by MacCallum's statements that "this liquefaction by means of a proteolytic ferment is exactly the process known as autolysis, except that it is recognized in that process that all tissues can tolerate in varying degrees of intensity the proteolytic ferment to dissolve their own cell bodies." He also refers to Dernby<sup>68</sup> as having shown that "in all tissues studied there are both pepsin-like and trypsin-like enzymes, etc." That hyperthermia by raising the digestive activity of these enzymes will tend to destroy the tissues containing them is self-evident.

The pathologic field covered by this greatly simplified conception of a very complex subject is almost bewildering. Cardiovascular diseases, particularly those of inflammatory origin and their complications, cause the bulk of our mortality; it has now exceeded, according to the international list of the 1914 Census, those of tuberculosis and pneumonia. Both of the latter great killers of mankind can also be shown to owe their great mortality in part to autolysis in most instances. We have seen that this applies also to the acute diseases of serous membranes, the pleura, peritoneum, etc. In various gastric, intestinal, pancreatic and hepatic diseases where contact with ferments prevails autolysis is a common source of lesions; typhoid, appendicular and colonic ulcerations are examples of its effects. The whole cerebrospinal system is subject to autolysis, as attested in part by the sclerosis and the paralyses they entail. This list, which could be greatly extended, sufficiently illustrates the importance of hyperthermia and autolysis in pathogenesis.

Here again we find the endocrine glands taking an active part in disease, but as morbid agents. The same organs, the adrenals, the thyroid and the pancreas impelled to excessive efficiency by a profound toxemia, destroy not only the pathogenic agency whatever it be, but also the affected tissues and often life itself.

**Cardiac Failure of Endocrine Origin as a Cause of Death.** While the adrenal secretion sustains pulmonary respiration and tissue oxidation, certain structures, the sympathetic system (whose ganglia and nerves contain the adrenal medullary principle) and the involuntary smooth muscular fibers, as shown by Oliver and

\* The prevailing idea, due to Eppinger, Falta and Rudinger, that adrenalin inhibits the pancreas, is due to an experimental error. As stated by Sollmann,<sup>64</sup> "the theory is not based on good evidence." MacCallum<sup>65</sup> also denies its correctness. R. G. Hoskins<sup>66</sup> has recently also condemned it.

Schäfer,\* the heart, the arterioles, and through the latter the muscular coats of the stomach, intestines, etc., are especially sensitive to its action. All these structures, therefore, are the first to feel the effects of excessive or deficient secretory activity of the adrenals. This selective effect is often an underlying cause of death due to adrenalin administered early in the course of anesthesia. Both chloroform (Aloi) and ether (Marchette) causing abnormal activity of the adrenals at first, the excess of adrenalin in the blood plus the adrenalin injected provoke such violent constriction of the arterioles that the sudden increase of vascular tension produced behind these terminal vessels causes cardiac arrest. Administered later, however, if cardiac failure occurs, adrenalin is very efficient because the adrenals have themselves become insufficient through the excessive secretory activity of the first and second stages. Preoperative injections of adrenalin in robust subjects have also caused death by adding an excess of adrenalin to the already abundant residual supply. Fear, excitement, anger, etc., may also prove lethal by inducing, doubtless in keeping with Cannon's theory, excessive secretory activity of the adrenals. Yet all these morbid effects are produced indirectly.

Far more frequently encountered in practice, however, is the condition previously referred to: That known generally as "adrenal insufficiency," and which I have termed "hypoadrenia." Quite in accord with the functions of the adrenals described its general symptomatology, subject to variations according to the causative condition, is briefly: Asthenia, great muscular weakness, extreme sensitiveness to cold, cold extremities, hypotension, weak cardiac action and weak pulse; anorexia, slowed basal metabolism rate, constipation and psychasthenia. Many of the perambulating cases of so-called idiopathic anemia are due to hypoadrenia, the pallor being mainly the result of vascular torpor and recession of the blood mass from the periphery to the splanchnic area.

The death-dealing influence of hypoadrenia manifests itself especially among the elderly. Histologic and vascular injection studies have conclusively shown that atrophy of the adrenals progresses steadily as age advances. Their vascular supply in a man of eighty years is hardly one-third that in one of thirty years—a condition which also prevails in the other endocrines. When, therefore, an infection strikes such a subject the defensive powers are such as to give it greater sway than in younger individuals, and the mortality is correspondingly greater.

A striking example of this condition is senile pneumonia which Charcot characterized as "the great enemy of old people." Refer-

\* My conception of the function of the adrenals sustains their theory, also the autotoxic theory of Abelson and Langlois and the emergency theory of Cannon, all of which, as stated, are normal manifestations of the fundamental function I attribute to these organs.

ring to its high mortality in subjects over sixty years of age, Osler also states, "From the reports of its fatality in some places one may say that to die of pneumonia is almost the natural end of old people." It may occur and prove fatal suddenly and unexpectedly right in the midst of the victims' occupations. Where, however, as in most instances, the disease develops gradually the symptoms are typical of failure, more or less rapid, of the adrenal functions. After a brief reaction to the infection, slight fever, very moderate rise of blood-pressure, no chill other than perhaps a chilly sensation, little if any cough and expectoration and no pain in the chest, there occurs, as Elsner<sup>69</sup> well described it, "rapid lowering of the arterial tension, marked lividity, edema of the lungs and extreme asthenia"—all typical signs of adrenal failure. As shown by Oliver and Schäfer in 1894, the adrenal secretion on its way to the lungs sustains the contractile power of the right heart. Elsner states that "dilatation of the heart, particularly of the right side, is a frequent complication of senile pneumonia"; he also records a fact of cardinal importance in the present connection, *e. g.*, that the dilatation of the right heart "sometimes precedes the infection," which means that the latter may be secondary to the adrenal failure.

Practically all acute infections may lead to a condition of the adrenals similar to that in senile pneumonia. It may supervene in lobar pneumonia at any age, in bronchopneumonia, typhoid fever, diphtheria, scarlatina, erysipelas, septicemia and in severe cases of measles, mumps and acute peritonitis—in a word, in all infections in which the febrile reaction is severe and prolonged. During the active early febrile process the adrenals, as shown in the section on the genesis of fever, secrete actively to carry on their part in the defensive function. Sooner or later, however, their efficiency weakens and the secretion produced is insufficient to carry on tissue oxidation and sustain the heart. This condition, which I have termed "terminal hypoadrenia," owing to its occurrence after the acute symptoms have ceased, gives rise to signs which differ but little if at all from those observed in senile pneumonia: Extreme lassitude, low blood-pressure, subnormal temperature, weak and rapid pulse, more or less dilatation of the heart and tendency to faint.

Terminal hypoadrenia thus illustrates a direct connection between the adrenals and a large number of general diseases. It also indicates that although functionally related with other ductless glands, the thyroid, pancreas, pituitary, etc., the adrenals are the most important organs of the endocrine group as far as symptomatology is concerned.

**Therapeutic Control of Endocrine Functions.** Molière, in his *Bourgeois Gentilhomme*, makes his candidate for patrician rank marvel at the fact that he had all his life been using prose. This

applies in a measure to the control of endocrine functions, which physicians have learned to do without realizing it. Thus the agents probably most used in practice today, the iodides, are now known to owe this property to the fact that their iodine is taken up by the thyroid gland to build up its secretion. I pointed this out in 1907,<sup>70</sup> and Marine and Williams<sup>71</sup> showed that the proportion of these salts taken up by the organ was constant in normal glands, but that this varied with the degree of hyperplasia present. Whether administered pure, as a salt, as a glandular product, or as Kendall's thyroxin matters not: The gland appropriates just what it needs, and, as this varies greatly with each patient, the initial dose should always be small.

Another agent in common use is strychnin: I urged in 1907<sup>72</sup> that this salt stimulated the adrenals. This was confirmed by Stewart and Rogoff<sup>73</sup> in 1919, who found that ordinary doses caused a marked and lasting increase in the production of adrenal secretion. When we recall that the adrenal principle is present in all sympathetic ganglia and nerves (and, according to my researches, in the axis-cylinders and cell bodies of all nerve cells, cerebrospinal and peripheral) we can well understand the almost ubiquitous use of strychnin by neurologists in atonic functional disorders. The same action, but to a less marked degree, obtains in the case of *nux vomica* and *brucine*.

Still another group is that represented by *digitalis*. Traube in 1871 showed that section of the spinal cord high up annulled the effects of *digitalis*, while Boehm<sup>74</sup> found that this procedure also arrested the effects of *digitalis* when they had become manifest. We have seen that, from my viewpoint, there is a nerve path from the pituitary *via* the basal tissues, cord and splanchnic to the adrenals. In 1917<sup>75</sup> I submitted that it was by stimulating the adrenals that *digitalis* produced its effects on the heart. In 1915 H. N. Richards and W. G. Wood<sup>76</sup> found that both *digitoxin* and *strophanthin* stimulated the "central nervous mechanism controlling the secretion of the suprarenal glands," and that this ceases "after section of the splanchnic nerves or of the spinal cord between the fourth and fifth cervical nerves," the section thus severing the path referred to above. *Apocynum*, *convallaria majalis* and *spartein*, from my viewpoint, act similarly upon the adrenals, though less actively than *digitalis*.\*

The action of the adrenal secretion upon cardiac tone, first shown by Oliver and Schäfer, is well known. Yet if the *digitalis* group actually affect the heart through the adrenals interruption

\* The London Lancet of September 25, 1920, editorially recommended the study of this phase of therapeutics, which I had termed "pharmacoenocrine therapy," by pharmacologic authorities when a committee appointed by the Minister of Health of Great Britain on the standardization of endocrine products would have finished its report.

of the secretion of the latter should impair its action. Stewart and Rogoff<sup>77</sup> found that compression of the adrenal veins, which carry the adrenal secretion to the inferior vena cava, the venous blood of which in turn takes it to the heart, caused arrhythmia, but that the heart resumed its normal action when the veins were released.

These few main agents suffice to indicate that the thyroid and adrenals can be stimulated by familiar remedies. Yet how account for this common action on the adrenals when the various drugs mentioned produce, as we all know, dissimilar pharmacologic effects? We have seen that the function of the adrenals is to carry on pulmonary and tissue respiration. Now, all adrenal stimulants, strychnin, digitalis, alcohol, ether, chloroform, caffeine, nicotine, turpentine, etc., as shown by well-grounded researches, increase respiration, but only in small doses, which vary considerably with each agent, and beyond which doses toxic phenomena appear. But they also produce other effects; they may act on the vasomotor center, the reflexes, the excretory organs, etc. Briefly, each drug is endowed with its own specific characters because of the variety of incidental effects it may produce. It is only when its stimulating action on the adrenals overtops all other effects that the specific phenomena due to this organ manifest themselves.

Organotherapy coöperates advantageously and on rational lines in this connection by increasing greatly the efficiency of the stimulating drugs used. Wherever there is hypothyroidism, thyroid gland alone is often efficient, but it becomes especially so if suprarenal gland and strychnin are also given, because hypoadrenia is likewise present. Strychnin by stimulating the adrenals causes them to appropriate the suprarenal gland administered more rapidly and to increase the metabolic rate earlier than when either agent is administered alone. Again, the heart failure of the aged fails totally at times to respond to digitalis, strychnin or any other agent. But the concomitant use of suprarenal gland to feed their atrophied adrenals soon changes the picture and will sustain the heart if persisted in. In senile pneumonia the very slow injection of seven minims of the 1-1000 adrenalin solution in a syringeful of saline solution administered intramuscularly every three hours is a powerful adjunct to the other measures used. This applies also to the cardiac failure or terminal hypoadrenia of all acute infections. Its power to save life under these conditions is striking. In chlorosis and other anemias in which iron is indicated the addition of suprarenal gland—provided it be active—favors the formation of hemoglobin, of which both it and the iron are constituents. These are, of course, but a few of a large number of our trusted remedies to which organic products become powerful helpmates.

Recalling the genesis of fever, we have seen that the digestive tryptic ferment owes its bacteriolytic and antitoxic activity to the liberation of heat through the coöperation of the thyroid and adrenal hormones and the cellular nucleins. Thus explained, the process accounts for several hitherto obscure effects, the therapeutic action of the heat, for instance, in its many forms. Heliotherapy is one of these. C. W. Saleeby,<sup>78</sup> in suggesting its study to the British Medical Research Council, credits Sonne, of Copenhagen, with the view that curative effect "is due to the capacity of the luminous rays during the light bath, to heat a very essential portion of the aggregate blood volume of the organism to a temperature possibly exceeding the highest fever temperature ever measured without causing the body temperature to rise to any appreciable degree." This deep penetration of sunlight harmonizes well with my conception of fever. Heliotherapy thus acts by supplying the tryptic defensive enzyme with the heat energy necessary to raise its bacteriolytic efficiency to its highest level, the adrenals and thyroid of the tuberculous child having acquired or inherited its liability to infection mainly through insufficiency of these two organs which manifests itself by inadequate development of heat energy. The vesperal fever is a protective reaction due to partial recuperation of the endocrines during the intervals. The beneficial effects of iodine early in tuberculosis are also explained, since it contributes to the heat-generating process while sensitizing the tubercle bacilli to the proteolytic action of trypsin.

Hyperthermia or pyrexia with all its dangers has also been met by the right measures: cold baths, even though their mode of action has not been understood. Briefly, by reducing the actual temperature through heat dissipation, the proteolytic activity of the defensive trypsin is antagonized. This explains also why the so-called "antipyretics" proved apparently so only, while in reality increasing the chances of death. After a primary stage of peripheral hyperemia they caused constriction of the arterioles, thus interfering with heat dissipation; in this manner they actually favored heat accumulation in the deeper tissues while the peripheral circulation was sufficiently embarrassed often as to cause cyanosis with formation of methemoglobin.

Another life-saving measure in addition to cold baths and other hydropathic uses of cold is the free use of saline solution with sodium bicarbonate added thereto in the proportion of 1 dram to 1 pint. It may be used as a pleasant beverage, equal parts with milk being ordered several times a day. By sustaining the osmotic properties of the blood and preventing abnormal viscosity and also acidosis, the kidneys are protected and the chances of both pyrexia and autolysis are materially reduced. The colonic use of saline solution and hypodermoclysis are also efficient in this direction.

Examples of the direct inhibitive control of the endocrines or



their effects are numerous. The use of quinin hydrobromide and ergotin in exophthalmic goiter, so effective in conjunction with rest, etc., is based upon its controlling influence upon the vascular supply of the thyroid, the adrenals and the thymus. The functions of an organ depending upon the proportion of arterial blood it receives, as shown by Claude Bernard, the functional activity of these glands is reduced correspondingly. The salicylates influence the endocrines in the same way. Arsenic is a potent agent in this direction. It inhibits, by a central action, the production of both the thyroid and adrenal hormones, and, as Cushny states, "lessens oxidation in the tissues," and therefore the results of abnormal proteolysis of the blood elements. Hence its great value in pernicious anemia.

One more example among the many which could be submitted is the direct antagonistic action of the nitrites to the constrictive action of the adrenal secretion upon the arterioles. Sollmann,<sup>79</sup> for instance, though unaware of their controlling influence over the suprarenal phenomenon, writes, "The fall of blood-pressure is due entirely to the extensive vasodilatation produced by the direct action of the nitrite on the arterioles." A life-saving measure suggests itself in this connection for cases such as those previously mentioned, in which adrenalin used early in the course of chloroform or ether anesthesia is added to the excess due to the adrenal stimulation caused by these anesthetics, tends to arrest the heart, viz., inhalations of amyl nitrite, which at once dilate the arterioles.

**Conclusions.** Why is the "endocrinology" of today in such a chaotic state? We have seen that the underlying cause is the prevailing obscurity concerning the physiologic functions of the endocrines. But Sir James Mackenzie<sup>80</sup> also wrote recently: "The conception of medical research which is dominant today is so immature and imperfect that it renders fruitless much of the research work. Indeed, so imperfect is the conception that fields essential to medical progress are not recognized." I might add that millions of dollars are being wasted on sterile researches and as many lives compromised through this arbitrary negation of newer fields simply because they do not appear to fit in with beaten though sterile paths.

While the foregoing study tends to sustain Mackenzie's criticism, it also affords evidence based on nearly twenty years' test to the effect that there is available a way of turning the tide. This is, as I have long urged, to *give the endocrines their due as major organs as important as any other in the body and to realize that they are mainly concerned with the preservation of life though capable, when functionally overactive, of causing death.* This has been exemplified by showing their participation in functions which, notwithstanding their overwhelming importance and much labor, had remained

obscure. There are over ninety other great problems\* quite as obscure and quite as important to human welfare which the endocrines can solve in conjunction with available data from all other branches of medical science.

Interpreted from my viewpoint, endocrinology imposes no sacrifice of what we know; it is eminently constructive in the sense that by filling gaps in all directions it finally solves problems of various kinds which, although near solution for decades, lacked precisely what the endocrines furnish to bring them to fruition. We have seen that the adrenals fill this role in pulmonary and tissue respiration, a cardinal physiologic function which had virtually remained *sub judice* six decades. We have seen also what the endocrines contributed to pathology by explaining four additional questions of the first importance, fever, pyrexia, hemolysis and terminal heart failure. As to therapeutics, the endocrines are fruitful in practically every phase of the subject studied as illustrated by the twenty and odd drugs and other remedial measures analyzed. Moreover, their study herein must have afforded some degree of surprise to the ultraconservatives referred to at the beginning of this address, by causing them to realize that they had all along been endocrinologists . . . but of the right kind. Their spirit of fairness should suggest, however, in view of the fact that they have so far been using the drugs and measures reviewed empirically, that the endocrines bid fair to place therapeutics on a scientific footing. Indeed, it looks as if it might in the end furnish medicine as a whole, and as a reward for the vast labor its development has imposed upon workers in all its branches, the last link it needed to place it upon the highest plane of efficiency.

#### REFERENCES.

1. Sajous, C. E. de M.: Active Coöperation between the Physiologist and the Clinician and Comparative Analysis of Coördinated Data in the Study of the Internal Secretions, *Endocrinology*, 1918, 2, 258.
2. Stewart, G. N.: Adrenal Insufficiency. *Endocrinology*, 1921, 5, 283.
3. Gley, E.: The Problem of the Adrenals, *New York Med Jour.*, 1921, 114, 9.
4. Swale Vincent: Recent Views of the Function of the Adrenal Bodies, *Endocrinology*, 1917, 1, 140.
5. Howell: Text-book of Physiology, 1918, 7th ed., p. 878.
6. Kendall, E. C.: The Function of the Thyroid-parathyroid Apparatus, *Jour. Am. Med. Assn.*, 1916, 66, 811.
7. Brubaker, A. F.: Text-book of Human Physiology, 1919, 6th ed., p. 499.
8. Howell: *Loc. cit.*, p. 880.
9. Schäfer: The Endocrine Organs, 1916, p. 123.
10. Swale Vincent: Internal Secretions and the Ductless Glands, London, 1913, p. 401.

\* The list of these leading features, ninety-six, was published in the introduction of the first eight editions, on page xii in the second volume of the first two editions and on the same page in the first volume of the following six editions of *Internal Secretions*. Despite the many years elapsed since they were first written the fundamental principles outlined would be subject to but few changes today if analyzed by the system described in the present paper.

11. Pawlow: *The Work of the Digestive Glands*, Thomson's translation, 1902, p. 46.
12. Swale Vincent: *Internal Secretions and the Ductless Glands*, London, 1913, p. 346.
13. Vulpian: Note sur quelques réactions propres à la substance des capsules surrénales, C. r. de l'Acad. des Sc., 1856, 43, 663.
14. Bert, Paul: Sur l'état dans lequel se trouve l'acide carbonique du sang et des tissus, C. r. de l'Acad. des Sc., 1878, 87, 628.
15. Barnes: *The Theory of Respiration*, Science, 1905, 21, 241.
16. Laulanié: *Eléments de Physiologie*, Paris, 1905, 2d ed., p. 377.
17. Bohr, C.: Ueber die Lungenathmung, Skand. Arch. f. Physiol., 1891, 2, 236.
18. Haldane and Lorrain Smith: The Absorption of Oxygen by the Lungs, Jour. Physiol., 1897, 22, 231.
19. Harley, Vaughan: The Effect of Compression on One Lung on Respiratory Gas Exchange, Ibid., 1899-1900, 25, 33.
20. Pembréy: Recent Advances in Physiology and Biochemistry, 1906, p. 519.
21. Vulpian: Loc. cit.
22. Cybulski, N.: On the Functions of Suprarenal Bodies, Gaz. Lekarska., 1895, 2 ser., 15, 299.
23. Langlois, P.: Le mécanisme de destruction du principe actif des capsules surrénales dans l'organisme, Arch. de physiol. normale et pathol., 1898, 10, 121.
24. Menten, M. L.: Action of Adrenalin on the Blood, Am. Jour. Physiol., 1917, 44, 176.
25. Jackson, D. E.: The Peripheral Action of Certain Drugs, with Special Reference to the Lung, Jour. Pharm. and Exper. Therap., 1913, 4, 291.
26. Dixon, W. E.: The Action of Adrenalin on the Bronchioles; A Demonstration, British Med. Jour., 1902, 2, 242.
27. Kariya and Tnaka: On the Hemolytic Action of Adrenalin, Jour. Tokyo Med. Assn., 1913, 26, No. 20; abstract in Sci-I-Kwai Med. Jour., 1913, 32, 10.
28. Menten and Crile: Studies on the Hydrogen-ion Concentration in Blood under Various Abnormal Conditions, Am. Jour. Physiol., 1915, 38, 225.
29. Menten: Loc. cit.
30. Byelaventz, P. P.: Action of Adrenalin on Living Organism, Rousskii Vrtel, 1903, 2, 247.
31. Bernstein and Falta: Ueber die Einwirkung von Adrenalin, Pituitrinum infundibulare and Pit. glandulare auf den respiratorischen Stoffwechsel, Verhandl. d. deut. Kongr. f. inn. Med., Wiesbaden, 1912, 39, 536.
32. Menten: Loc. cit.
33. Tompkins, Sturgis and Wearn: Studies on Epinephrin: The Effects of Epinephrin on the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Man, Arch. Int. Med., 1919, 24, 269.
34. Sandiford, I.: The Effect of the Subcutaneous Injection of Adrenalin Chloride on the Heat Production, Blood-pressure and Pulse-rate in Man, Am. Jour. Physiol., 1920, 51, 407.
35. Januschke and Pollak: Zur Pharmakologie der Bronchialmuskulatur, Archiv f. exper. Path. u. Pharm., 1911, 66, 205.
36. Née, Rock and Courtright: The Influence of Adrenalin on Respiration, Am. Jour. Physiol., 1914, 34, 326, 331.
37. Mulon: Personal Communication.
38. Battelli, M. F.: Présence d'adrénaline dans le sang d'animaux normaux. Son dosage, C. r. de la Soc. de Biol., 1902, 54, 1179.
39. Oliver and Schäfer: The Physiologic Effects of Extracts of the Suprarenal Capsules, Jour. Physiol., 1895, 18, 230.
40. Morel, I. E.: L'Adrénaline. Le progrès méd., 1903, 32, 65, 81.
41. Lépine, R.: Sur l'action de l'extrait de capsules surrénales, Semaine méd., 1903, 23, 53.
42. Reichert, E. T.: Adrenalin, the Active Principle of Adrenal Extract, a Proposed Agent in Morphin and Opium Poisoning, in Circulatory Failure, in the Prevention of Collapse in Anesthesia and in Allied Conditions, Univ. Penna. Med. Bull., 1901-1902, 14, 51.
43. Courmont: Congrès de Méd. interne, Montpellier, 1898.
44. Bra. Cited by E. W. Adams: The Results of Organotherapy in Addison's Disease, Practitioner, 1903, 71, 472.
45. Jaboulay: La greffe de corps thyroïde et de capsules surrénales dans les maladies de ces glandes, Lyon méd., 1897, 84, 399.

46. Israel, J.: Ueber Fieber bei Malignen Nieren- und Nebennierengeschwülsten, Deut. med. Wehnschr., 1911, 37, 57.
47. Sandiford, I.: Loc. cit.
48. Tompkins, Sturgis and Wearn: Loc. cit.
49. Addis, Barnett and Shevsky: The Regulation of Renal Activity, Am. Jour. Physiol., 1918, 46, 39.
50. Aub, Forman and Bright: The Effect of Adrenalectomy upon the Total Metabolism of the Cat, Ibid., 1921, 55, 293.
51. Bovier and Shevsky: Urea Excretion after Suprarenalectomy, Ibid., 1919-1920, 1, 191.
52. Review: Wiener klin. Rundschau, 1913, 17, 420.
53. Weil: Die Innere Secretion, Berlin, 1921, p. 140.
54. Halliburton: Text-book of Physiology, 1911, 10th ed., p. 392.
55. Barlow, Lazarus: General Pathology, 1904, 2d ed., p. 435.
56. MacCallum: Text-book of Pathology, 1920, 2d ed., p. 159.
57. Justus, J.: Ueber den physiologischen Jodgehalt der Zelle, Virchows Arch., 1903, 176, 1.
58. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, 1903-1922, all editions, pp. 960-1008.
59. Stewart and Rogoff: The Relation of the Spinal Cord to the Spontaneous Liberation of Epinephrin from the Adrenals, Jour. Exper. Med., 1917, 26, 613.
60. Lévi and Rothschild: Physiol. de la glande thyroïde, Paris, 1910.
61. McCarrison, R.: The Etiology of Endemic Goiter, Lancet, 1913, 1, 365.
62. Rendu, J.: Hyperthermie dépassant 43° pendant plusieurs jours; guérison, Lyon méd., 1900, 93, 331.
63. Christian and Walker: Experimental Endocarditis Produced by Drugs, Tr. Am. Soc. Adv. Clin. Investig., Boston Med. and Surg. Jour., 1910, 162, 901.
64. Sollmann, T.: Manual of Pharmacology, Philadelphia, 1917, p. 334.
65. MacCallum, W. G.: The Internal Secretion of the Pancreas, Jour. Am. Med. Assn., 1911, 56, 655.
66. Hoskins, R. G.: Some Current Trends in Endocrinology, Jour. Am. Med. Assn., 1921, 77, 1459.
67. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, Philadelphia, 1922, 10th ed., p. 34.
68. Darnby, K. G.: A Study on Autolysis of the Animal Tissues, Jour. Biol. Chem., 1918, 35, 179.
69. Elsner, H. I.: Pneumonia in the Aged, New York State Med. Jour., 1909, 9, 34.
70. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, Philadelphia, 1907, 2, p. 1159.
71. Marine and Williams: The Relation of Iodin to the Structure of the Thyroid Gland, Arch. Int. Med., 1908, 1, 349.
72. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, 1907, 2, 1225.
73. Stewart and Rogoff: The Action of Drugs upon the Output of Epinephrin from the Adrenals. I. Strychnin. Jour. Pharm. and Exper. Therap., 1919, 13, 95.
74. Boehm, R.: Untersuchungen über die physiologische Wirkung der Digitalis und des Digitalin, Arch. f. d. ges. Physiol., 1872, 5, 153.
75. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, 1907, 2, 1215.
76. Richards and Wood: The Action of Strophanthin upon Suprarenal Secretion, Jour. Pharm. and Exper. Therap., 1915, 6, 283.
77. Stewart and Rogoff: Demonstration that the Spontaneously Liberated Epinephrin Can Exert an Action upon the Heart, Ibid., 1919, 13, 397.
78. Saleeby, C. W.: More Light: The Need for a Coordinated Inquiry into the Physiology and Therapeutics and Hygiene of Sunlight, Medical Press and Circular, 1922, new series, 113, 29.
79. Sollmann: Loc. cit., p. 376.
80. Mackenzie, Sir James: A Defence of the Thesis that the Opportunities of the General Practitioner are Essential for the Investigation of Disease and the Progress of Medicine, British Med. Jour., 1921, 1, 797.

## A RÉSUMÉ OF OUR KNOWLEDGE OF THE FUNCTIONS AND INTERRELATIONS OF THE ENDOCRINE GLANDS.\*

BY FRANCIS ASHLEY FAUGHT, M.D.

AND

THOMAS J. RYAN, M.D.

PHILADELPHIA.

THIS report is based upon a review of recent literature, together with an examination of a number of recent works upon the endocrine glands.†

In the preparation of this review we have endeavored to include only those contributions which on investigation appeared to have either sound clinical or experimental foundations, excluding as far as possible all unreliable, fantastic and purely hypothetic material, in which the literature unfortunately abounds.

To follow a definite plan in the presentation of the data relating to each gland has been found impossible, because of our failure to find sufficient reliable material relating to some of them.

The first significant conclusion reached in the study of these organs is the apparent fact that each possesses a definite period of activity during which it appears to exert powerful metabolic influences over various portions of the organisms.

With this thought in mind, Walter Timme,<sup>1</sup> in a recent article, happily groups the internal secretory glandular system by dividing mankind, endocrinologically speaking, into three epochal periods: The first, presided over chiefly by the thymus and the pineal, embracing the span of years from birth to puberty (period of growth and development); and second, between puberty and prime (years of aggression, activity and reproduction) is under the domain of the gonads, whose control is, however, greatly assisted and considerably modified both here and in the later portion of the first period by the thyroid, the pituitary and the adrenals; and the third, the period of general deterioration (involution to dissolution), marked by gradual diminution in the activity of the whole endocrine system.

**The Thyroid Gland.** Concerning the thyroid gland we find that while all authorities admit the powerful influence of this organ on general metabolic processes, and while it is generally supposed that the iodine-colloid constituent of the thyroid gland is its specific secretion, nevertheless there is no conclusive data by which the presence of a specific autocoid can be assigned to this gland, in spite

\* Read before the West Branch of the Philadelphia County Medical Society, February 14, 1922.

† Complete bibliography omitted, only direct references will be found in the article.

<sup>1</sup> Neur. Bull., 1921, 1, 83.

of the splendid work of E. C. Kendall,<sup>2</sup> who has succeeded in isolating from the non-protein iodine-colloid of the thyroid a pure crystalline substance of constant composition containing over 60 per cent of iodine, which has been called thyroxin, and which he believes to be the active constituent of this gland. As to whether this iodine-containing material is manufactured within the gland itself or whether the thyroid simply acts as a storehouse for iodine for the rest of the body has not been determined, Falta<sup>3</sup> and Kraus holding opposing views.

Ardent exponents of the *interrelation* of the glands of internal secretion have gone so far as to suggest thyroidectomy for the relief of diabetes mellitus where associated with evident thyroid hyperfunction. This pernicious theory is opposed by Fitz,<sup>4</sup> who reports 39 cases of diabetes mellitus associated with hyperthyroidism in whom thyroidectomy and the roentgen-ray failed to influence the glycosuria to any appreciable degree or for any reasonable length of time.

*Thyroid to Parathyroid.* A reciprocal function between the thyroid and the parathyroids was first suggested by Vincent and Jolly<sup>5</sup> after their experimental demonstration of hypertrophy of the parathyroids and the appearance of colloid material between their cells after removal of the thyroid. Blair Bell does not wholly concur in this view, while Macleod<sup>6</sup> has gone so far as to assign entirely distinct functions to the thyroid and the parathyroids. This opinion being based, in part at least, upon the work of Paton and Findlay,<sup>7</sup> who present evidence to show that the parathyroids exert their action mainly on and through the nerve centers, while the thyroid exerts its function primarily on metabolic processes through the blood stream. More recently Vincent and Arnason<sup>8</sup> have reinvestigated this problem without finding any experimental evidence to support Vincent's previous view that the parathyroids remaining after thyroidectomy become hypertrophied or develop characteristics of thyroid tissue.

*Thyroid to Pituitary.* An intimate relationship between the thyroid gland and the pituitary is generally accepted. This is shown by (a) the formation of colloid masses, not normally present in the pituitary, following thyroidectomy, this colloid assuming the same staining characteristics as the thyroid colloid; (b) the similarity of the structural changes occurring in diseases of the thyroid and of the pituitary; (c) the observation of Bell and others that removal of the thyroid increases the secretory activity of all

<sup>2</sup> Med. Clin. North America, 1919, 3, 3, 583.

<sup>3</sup> The Ductless Glandular Diseases. P. Blakiston's Son Co., 1915.

<sup>4</sup> Arch. Int. Med., March 15, 1921, p. 305.

<sup>5</sup> Jour. Physiol., 1905, 32, 65; 1906, 34, 295.

<sup>6</sup> Physiology and Biochemistry, 3d edit., C. V. Mosby Co., 1920.

<sup>7</sup> Quart. Jour. Exper. Physiol., 1916, 10, 214.

<sup>8</sup> Endocrin., 1920, 4, 199.

parts of the pituitary; (d) the close neurologic relationship as shown experimentally by stimulation of the sympathetic, which causes an increase in secretion of the adrenals, thyroid and pituitary;<sup>9</sup> (e) the close embryologic relation of these two glands; the thyroid and the glandular portion of the pituitary both arising from outgrowths of the entoderm lining the floor of the pharynx, where they are closely connected until the third month of embryonic life.

*Thyroid to Ovaries.* The close physiologic relationship between the thyroid and ovaries has been long known. This is well shown by (a) the frequent enlargement of the thyroid at puberty, during pregnancy and at the climacteric; (b) the prevalence of menstrual disturbances accompanying both hypofunction and hyperfunction of the thyroid; (c) by the fact that thyroidectomy is followed by atrophy of the uterus; (d) because deficiency of the thyroid in early youth or the removal of the thyroid in early youth or in young animals prevents the normal development of the sex glands. Finally, castration has been shown by Bell and Hick<sup>10</sup> to favorably modify the profound metabolic crisis seen after thyroidectomy.

*Thyroid to Suprarenals.* Notwithstanding the statement of Bell<sup>11</sup> that in three of his experimental animals he noted an increase in secretory function of the suprarenal cortex following thyroidectomy, we are forced to conclude with Macleod<sup>12</sup> that reliable experimental evidence has so far failed to show any definite relation between the thyroid and the suprarenals.

*Thyroid to Thymus.* The persistence of the thymus gland in exophthalmic goiter as well as the known anatomic and embryologic relationship of these two glands suggest their close physiologic association, although this has not yet been proven by reliable experimental or physiologic work. (*Vide infra.*)

*Comment.* Viewed in the light of the foregoing conclusions the question naturally arises: Is there an internal secretion of the thyroid? or does the gland exert its influence on the pituitary, parathyroids, ovaries and thymus through an interrelated nervous mechanism? In this connection some authorities have even gone so far as to question whether even the toxic symptoms of so-called toxic goiter are the result of hypersecretion of the thyroid (Marine and Lenhart<sup>13</sup>).

Opposed to the toxic theory, Macleod<sup>14</sup> cites the following experimental evidence: (a) The injection into animals of the blood of patients suffering from thyroid hypersecretion is not followed by evidence of any toxicity characteristic of hyperthyroidism; (b)

\* W. Langdon Brown: *The Sympathetic Nervous System in Disease*, Henry Frowde, Hodder & Stoughton, Ltd., London, 1920, p. 161.

<sup>9</sup> *British Med. Jour.*, 1902, 1, 157.

<sup>10</sup> *The Sex Complex*, William Wood & Co., 1916, p. 51.

<sup>11</sup> *Loc. cit.*, p. 788.

<sup>12</sup> *Arch. Int. Med.*, 1911, 8, 265.

the administration of an extract of a gland removed from an exophthalmic case had no different physiologic action upon a normal animal than an extract from a normal gland containing the same percentage of iodine; (c) degenerative and pigmentary changes in the ganglion cells of the cervical sympathetic have been found in cases of exophthalmic goiter and are believed by Wilson<sup>15</sup> to be characteristic of this condition. For these reasons disease of the sympathetic system may well be assigned the etiologic role in the production of the cardiac and ocular symptoms as well as the thyroid hypertrophy secondary to which the metabolic phenomena characteristic of this disease naturally follow.

**The Pituitary.** It is usually accepted that the anterior lobe of the pituitary gland is chiefly concerned in maintaining and regulating body growth, particularly of the skeletal portion, and in addition entering into the metabolic activity concerned in the establishment of puberty and sexual maturity. The posterior lobe is assumed to be active in the production of a powerful auto-coid which is closely concerned with the physiologic activity of unstriated muscle, while the pars intermedia is believed to be associated with the posterior lobe in the production of this auto-coid. We have not been able to accept these statements without considerable reservation, since the literature abounds in clinical and experimental evidence which cannot be wholly reconciled to this belief. Thus, Frank,<sup>16</sup> correlating the work of a number of investigations relative to the influence of the pituitary extract to the development of the genital tract, concludes that this substance has not been shown to stimulate the development of the female sex organs, and has very little if any effect upon those of the male.

The most striking thought relating to the modern conception of the functions of this gland comes from Dr. Sajous, who recently stated that there is no reliable evidence to show that the pituitary produces any internal secretion, the statements of many observers and the deductions of Cushing notwithstanding. Sajous supports this revolutionary theory by bringing forward abundant experimental and clinical evidence to show that (a) the administration of anterior lobe extract never has been shown to affect the growth of children;<sup>17</sup> (b) the anterior part, which is said to be the active agent controlling the histologic growth of the body, presents no microscopic evidence of secretory tissue; (c) there has never been any reliable demonstration of a secretion from this lobe; (d) the relation of the pituitary to acromegaly cannot be substantiated, since were this affection the result of a perverted

<sup>15</sup> AM. JOUR. MED. SC., 1916, 152, 799.

<sup>16</sup> Jour. Am. Med. Assn., 1919, 73, 1764.

<sup>17</sup> R. Klinger: Arch. f. d. ges. Physiol., 1919, 177, 232.

<sup>18</sup> P. E. Smith: Anat. Record, Philadelphia, 1921, 21, 83.



secretory activity the results could neither be unilateral nor localized;<sup>19</sup> (c) that clinical and experimental evidence shows that pressure on the tuber cinereum produces the same effect as pituitary disease. To this we might add that an extensive study of the effect of pituitary opotherapy in experimental diabetes insipidus by Camus and Roussy,<sup>20</sup> who show that the polyuria usually attributed to a lesion of the pituitary is in reality due to a lesion in the base of the brain. Sajous's present hypothesis is, therefore, that the pituitary organ operates through the agency of a demonstrated nervous relationship by way of the splanchnics, such activity being possible because the posterior pituitary lobe is in reality the main ganglion of the sympathetic, which controls the thyroid, the adrenal and the thymus and coördinates them.

*Pituitary to Thyroid and Ovaries.* Relationship between the thyroid and pituitary is shown by the fact that the removal of either gland produces strikingly similar effects upon the sexual functions and the general development of young animals, although according to Robertson, Goetsch and others<sup>21</sup> the administration of pituitary extract produces no stimulating effect upon the development of the sex organs, at least in females.

Additional proof is found in the fact that when the condition known as hypopituitarism is experimentally produced the thyroid and thymus glands enlarge, while the cortex of the suprarenals and the sex glands fail to develop. In adults clamping or separation of the stalk results in intense atrophy of the uterus and of the ovaries, while at the same time the thyroid enlarges and its colloid content increases.

*Pituitary to Suprarenal.* The assumption that there exists a definite relationship between these two glands appears to be based upon the statements of observers, who based their opinion solely upon the supposed similarity of physiologic action of the extracts of the two glands. More recent physiologic experiments question this relationship because it has been shown that pituitary and suprarenal gland extracts are dissimilar in their action; thus pituitrin acts directly upon the involuntary muscle fibers themselves while epinephrin acts solely upon the receptor substance associated with the terminations of the sympathetic nerve fibers in the involuntary muscles.<sup>22</sup> As to a definite endocrine relation, clinical and experimental evidence is generally conflicting. Such authorities as Cushing<sup>23</sup> and Bell<sup>24</sup> take opposite views, the former stating that partial pituitary destruction leads to a definite hyperplasia of the suprarenal, while the latter was unable to demonstrate such an effect.

<sup>19</sup> C. Bellavitis: *Abstract Endocrin.* 1921, 5, 653.

<sup>20</sup> *Comp. rend. Soc. de Biol., Paris*, 1920, 83, 1578-1583.

<sup>21</sup> Editorial, *Jour. Am. Med. Assn.*, 1917, 69, 1697.

<sup>22</sup> J. J. R. Macleod: *Loc. cit.*

<sup>23</sup> *The Pituitary Body and its Disorders*, 1st edit., J. B. Lippincott Company.

<sup>24</sup> *Loc. cit.*

*Pituitary to Pancreas.* Because of the influence of pituitrin upon carbohydrate metabolism, which is thought to be primarily controlled by the islands of Langerhans, effort has been made to establish an endocrine relation between these two glands; thus Kraus<sup>25</sup> states that after removal of the pancreas in cats (a) the eosinophil cells of the hypophysis disappear. These cells also disappear in juvenile diabetes; (b) the thyroid first hypertrophies and then becomes smaller; (c) the lipid disappears from the cortex of the adrenals while the medulla stains more deeply with chromic acid; (d) the gonads and the pineal become smaller and (e) the parathyroids show no change; on the other hand many carefully conducted investigations do not corroborate these findings, so that the presence of any endocrine relation is still in doubt.

*Pituitary to Parathyroid.* Nothing definitely known.

**The Suprarenal Glands.** *Anatomy and Physiology.* Our knowledge of the suprarenals is most complete, because these organs lend themselves best to methods of experimental study.

The suprarenals are made up of two embryologically independent parts—the external portion, or the cortex, and the internal portion, or the medulla. The intermediary zone belongs to the cortex. The cortex is composed of columns of cells containing highly refractive lipid granules. The medulla is richly supplied with nerves and multipolar ganglion cells, and in addition nests of cells which take a brown color when stained with chromic acid, because of which they are termed chromaffin cells. This chromaffin tissue is supposed to produce a highly complex compound which is chemically related to albumin, tyrosin and phenylalanin, known as suprarenalin or adrenalin. Experimental study shows that adrenalin acts only on the purely sympathetic nerve-endings, especially on the so-called musculoneural junction.

The important physiologic properties of adrenalin are: (a) An ability to elevate blood-pressure by constricting the peripheral vessels without the assistance of the splanchnic innervation;<sup>26</sup> (b) inhibition of the musculature of the intestines, the stomach, the esophagus, the gall-bladder, the urinary bladder, also of such glandular structures as the lacrimal, the salivary, the mucous glands of the mouth and pharynx and the gastric glands; (c) an accelerator of the three sphincters (the pyloric, the ileocecal and the internal sphincter of the anus); (d) glycogenolysis, as shown by the production of glycosuria and hyperglycemia after its intravenous injection, and (e) shortening of the clotting time of the blood. It is worthy of note that most of these physiologic activities find their counterpart in the sympathetic and follow experimental stimulation of the sympathetic nerve supply to these organs.

<sup>25</sup> E. J. Kraus: München. med. Wehnschr., 1921, 68, 794.

<sup>26</sup> W. Löffler: Schweizer Arch. f. Neurol. u. Psych., Zürich, 1921, 8, 163-181; Abt. Endocrin., 1921, 5, 803.

This similarity of action between adrenalin and the sympathetic system is explained, on the basis of comparative anatomy and embryology, by the fact that the chromaffin tissue found in the suprarenals originates in an outgrowth of the neuroblast from which is laid down the primitive ganglia of the posterior roots, masses of cells being split off which become the common ancestors of the sympathetic ganglia and the chromaffin system.

*Adrenals to the Thyroid and Parathyroid.* There is no reliable data to prove a hormonie relationship between the adrenals and the thyroid and the parathyroids, although relationship between the adrenals and thyroid has been asserted, because thyroid feeding is said to produce hypertrophy of adrenals. Opposing this view it has been shown by Gley,<sup>27</sup> Carlson<sup>28</sup> and Stewart and Rogoff<sup>29</sup> that thyroideectomy causes a similar hypertrophy.

*Adrenals to the Sex Glands.* Embryologically the close relation of the adrenals to the sex glands is well known. Such an association is well supported clinically by the fact that in cases of sexual precocity the adrenal cortex has been shown to be hypertrophied, while certain tumors of the adrenal cortex in young children not producing destruction of the gland are generally associated with premature development of the secondary sexual characteristics. In addition, hypertrophy of the adrenal cortex during pregnancy is an established fact. Furthermore, in hyperplasia of the adrenals changes occur in the testicles, particularly in the interstitial cells, although experimental castration has not been shown to have any constant effect upon the adrenal cortex.

No relationship between the medulla of the adrenals and the sexual organs has yet been established.

*The Adrenal to the Pituitary.* As already discussed under the head of the pituitary no definite physiologic or hormonie relationship has yet been established between these two glands, although Blair Bell<sup>30</sup> states that after partial removal of the adrenals the pars anterior cells show certain alterations in staining characteristics which he believes indicates an increased activity of the pituitary.

Concerning the other glands of internal secretion we have been unable to find any evidence of correlation with the adrenals.

*The metabolic relation* of the adrenals is important, as shown by the fact that the injection of epinephrin in normal animals is followed by hyperglycemia and glycosuria. This is explained by the demonstrated ability of epinephrin to convert glycogen into glucose. This glycogenolytic function is believed to be dependent primarily upon the action of the sympathetic mechanism, the

<sup>27</sup> Arch. internat. de physiol., 1914, 14, 175-191.

<sup>28</sup> Jour. Am. Med. Assn., 1916, 67, 1484.

<sup>29</sup> Am. Jour. Physiol., 1921, 5, 569.

<sup>30</sup> Loc. cit.

normal functional activity of which is maintained only by the presence of a proper concentration of adrenalin in the circulating blood. Additional metabolic activity of this gland is shown by an increase in calcium, phosphorus and urea elimination after experimental removal of one of the adrenals.

**The Parathyroids.** Embryologically the parathyroids are entodermal glands having a common origin with the thymus from the branchial arches in close association with the origin of the thyroid. The so-called *epithelial bodies* of the parathyroids develop from the dorsal part of the third and fourth branchial pouches.

Functional independence of the parathyroids was for a long time unrecognized because this intimate relation above described permitted these glands to be in direct contact with, or even included within, the body of either the thymus or the thyroid, or both. More recent studies and investigations have demonstrated the individual functional activity of these glands. Paton,<sup>31</sup> for example, claims that complete experimental deficiency of the thyroid does not produce any of the symptoms of tetany, while deficiency of the parathyroids is not made good by thyroid therapy, and finally extirpation of the parathyroids alone disturbs calcium metabolism, with the production of tetany but without the production of myxedema.<sup>32</sup>

There is neither clinical nor experimental evidence to prove the existence of a specific parathyroid hormone. The parathyroids are concerned mainly with exercising a restraining or inhibitory influence over certain nerve centers and in controlling to some degree the calcium metabolism.

Hypoparathyroid activity results in disturbed calcium metabolism accompanied by a loss of calcium from the blood and nervous tissues with the production of tetany.<sup>33</sup>

**Sex Glands.** Embryologically and anatomically the sex glands of the male are usually separated into two distinct functional parts, *i. e.*, the reproductive portion and the interstitial gland, or so-called "interstitial tissue of Leydig," which is described as epithelioid cell accumulations imbedded in the sex glands of the male. These cell accumulations contain acidophilic and basophilic granules very similar to the cells of the suprarenal cortex, and like them are of mesodermal origin.<sup>34</sup> In women we understand by the term "interstitial gland" a cell complex developing from the atretic follicles of the theca interna.

It was formerly thought that the interstitial glands controlled the development of the primary and secondary sex characteristics and were therefore of great importance in determining general body conformation. Opposed to this view Meyer<sup>35</sup> states that

<sup>31</sup> Quart. Jour. Exp. Physiol., 1916, 214.

<sup>32</sup> W. Falta: Loc. cit., p. 176.

<sup>33</sup> J. J. R. Macleod: Loc. cit., 801.

<sup>34</sup> Zentralbt. f. Gynec., 1920, 16, 593.

<sup>35</sup> W. Falta: Loc. cit. p. 370.

an interstitial gland in women does not exist, that there is no increase in these special cells in girls at puberty, that these cells are found in embryo at the sixth fetal month and these cells have nothing to do with sexuality, and, further, that the ovaries are not essential to the development of the secondary sex characteristics.

Conclusive evidence of the existence of a specific autocoid elaborated by the interstitial gland is so far wanting, it being probable that the influence of these glands on body growth and the sexual characteristics is very slight, since the great mass of reliable evidence assigns the control of the primary and secondary sexual characteristics to well-demonstrated influences from the other ductless glands.<sup>36 37</sup>

*Sex Glands to Pituitary, Thyroid and Adrenals.* Physiologic relation of the ovary to the pituitary, thyroid and adrenals is demonstrated by abundant experimental and clinical evidence of an increased activity of the pituitary, the thyroid and the adrenals during pregnancy and by the marked changes in the sexual glands and alterations in their normal period of development in pathologic conditions affecting the pituitary, adrenal and thyroid glands (see above).

**Thymus.** While there is still active discussion as to whether the thymus should be included in the group of glands of internal secretion it seems reasonable in the light of the more recent literature to agree with Falta that, since it has been proven that the gland rapidly atrophies at puberty in both sexes, and since experimental removal of the ovaries in young animals is followed by rapid sexual development and a limitation of *somatic growth*, the theory of the presence of an internal secretion is tenable. Bucher<sup>38</sup> reports 8 cases in which thymectomy in children was followed by disturbance in growth and warns against thymectomy or roentgen-ray of the whole gland. The thymus, therefore, probably is closely related to the sex glands, upon which it influences a restraining action during the early years of life. This action is seen clinically in cases of thymic subinvolution, in which sex differentiation is incomplete and development of these organs arrested, while the skin is soft in texture, smooth and velvety with a fine covering of hair, while in the male there is little or no mustache or beard; the pubic hair likewise is sparse in both sexes, and in the male assumes the female characteristic distribution. The menses may be delayed or entirely lacking.<sup>39</sup>

**Pineal.** The function of the pineal gland is obscure. In cases in which its removal has been successfully accomplished (in the fowl) it has been found that body growth was stimulated and that

<sup>36</sup> Blair Bell: Loc. cit., p. 145.

<sup>37</sup> Blair Bell: Abstract Endocrin., 1921, 5, 660.

<sup>38</sup> Schweizer Arch. f. Neurol. u. Psych., Zurich, 1921, 8, 208-215.

<sup>39</sup> W. Timme: Neur. Bull., 1921, 3, 1-3, and Address before Philadelphia Pediatric Society, December 3, 1921, author's notes.

the sexual characteristics developed more quickly.<sup>40</sup> This study would seem to indicate that when new growths affecting the pineal gland are accompanied by precocious sexual development, due to hypofunction of this organ, and that therefore this gland maintains in some obscure way an inhibitory influence upon the development of the sexual organs. On the other hand, Sisson and Finney,<sup>41</sup> in a series of carefully conducted and controlled experiments on rats, failed to find that feeding pineal powder in large doses in any way influenced the growth, nutrition or sexual characteristics or sexual development of the test animals.

No histologic or experimental evidence has yet been produced to demonstrate an internal glandular function of the pineal body.

**Pancreas.** The many experimental studies that have been performed in an effort to demonstrate the presence of a specific internal secretion of the pancreas have so far been unsuccessful. No secretion has yet been isolated or defined chemically; neither are we certain as to the path through which, if such be present, it is given off. Owing to the extreme vascularity of the pancreas it has been suggested that a substance may be given off bound to the blood corpuscles. Those who have argued for an internal secretion from this gland assign to the islands of Langerhans this supposititious role, because experimental evidence makes the functional independence of the insular apparatus highly probable.<sup>42</sup>

**Spleen.** The discussion would not be complete without reference to recent literature bearing on the probable existence of an internal secretion elaborated by the spleen. Nathan B. Eddy<sup>43</sup> reviews the literature to date and appends a bibliography of forty-nine references. After a careful discussion of all pertinent data Eddy concludes that the hypothesis that the spleen produces an internal secretion is supported by (a) the changes noted in the erythrocytes after splenectomy; (b) the modification of the blood picture in hyperplasia of the spleen ameliorated in some cases by splenectomy, and (c) the specific effects on the red blood corpuscles produced by the injection of splenic extract.

The result of this study has been rather discouraging, because of the persistent recurrence of contradictory results in the experimental work done by equally competent observers, which forces the conclusion that despite the great amount of work done, the undoubted accuracy of the evidence presented and the apparent reliability of the deductions based upon them we actually know but a small fraction of what is yet to be learned of the functions and correlations of this interesting group. The opinion is further strengthened by the fact that in much of the clinical evidence there is often no firmer foundation than the enthusiasm of the self-styled endocrinologist.

<sup>40</sup> J. J. R. Macleod: *Loc. cit.*, p. 520.

<sup>41</sup> W. Falta: *Loc. cit.*

<sup>42</sup> *Jour. Exper. Med.*, 1920, 31, 335.

<sup>43</sup> *Endocrin.*, 1921, 5, 461.

## AURICULAR FLUTTER, WITH REPORT OF CASES.

BY JOHN H. KEATING, M.D.,

AND

JOSEPH HAJEK, M.D.,

NEW YORK.

(From St. Luke's Hospital Medical Service, S. W. Lambert, M.D., Director, Electrocardiographic Department, and Cardiac Clinic.)

THE term "auricular flutter" was first applied by McWilliams in 1887, and the designation has been retained up to the present time. Since the advent of the electrocardiograph the condition has been recognized with far greater frequency.

The first experiments reported from the laboratory were published by McWilliams.<sup>1</sup> He first observed the rapid response to faradization on the auricles of a dog and a cat, and, as he says, "the application of faradic current sets the auricle into a rapid flutter, no distinct signs of incoördination (being) present." The foregoing experiments of McWilliams differed, therefore, from experiments on voluntary muscle in that faradization of voluntary muscle produces tetanus, whereas faradization of cardiac muscle produces a series of rapid, coördinated contractions. This difference is due in part to the fact that in the heart muscle a comparatively long inhibitory period follows upon each ventricular contraction, during which the heart is not able to respond to any stimulus, while a second factor is found in the sphincter-like arrangement of the muscle fibers around the openings of the superior and inferior venæ cavæ. The length of the inhibitory period peculiar to each auricle will naturally influence the speed of its flutter. Consequently, some auricles will flutter at the rate of 200 per minute, others at 300. According to Lewis,<sup>2</sup> the highest ever observed in man was 335. One of our cases, as the record shows (Fig. 11), attained a speed of 360 per minute, and at times the rate increased to 375.

Clinically the term auricular flutter was first applied by Jolly and Ritchie,<sup>3</sup> in 1905, in the report of their case of auricular flutter associated with complete heart-block.

## REPORT OF CASES

CASE I.—E. H., aged fifty-six years, laundry worker, entered the hospital November 8, 1916, and was discharged one month later (December 8) improved. On admission she was complain-

<sup>1</sup> Jour. Phys., 1887.

<sup>2</sup> Heart, 1910-11, 2, 177.

<sup>3</sup> Lancet, 1912, 2, 1418.

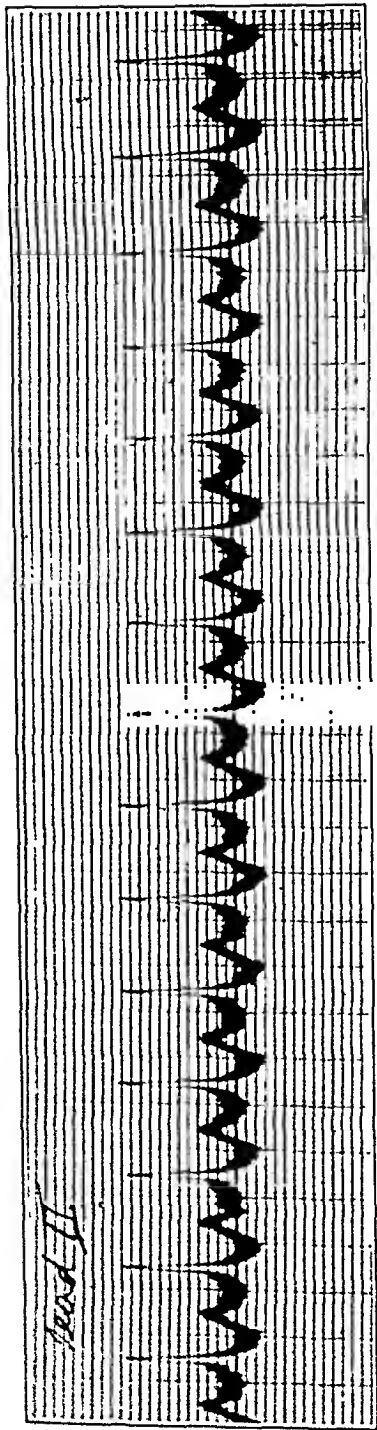


FIG. 1 (Case I).—Electrocardiogram on admission November 8, 1916, showing auricular flutter. Auricular rate 300. Ventricular 150. Time in fifths of a second.

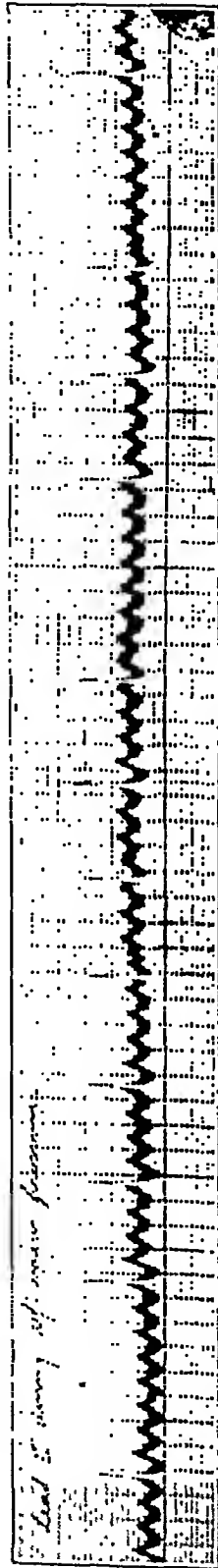


FIG. 2 (Case I).—Curve of the same patient, showing effect of left vagus pressure. Auricle uninfluenced. Ventricle slowed from 3:1 to 8:1. Time in fifths of a second.

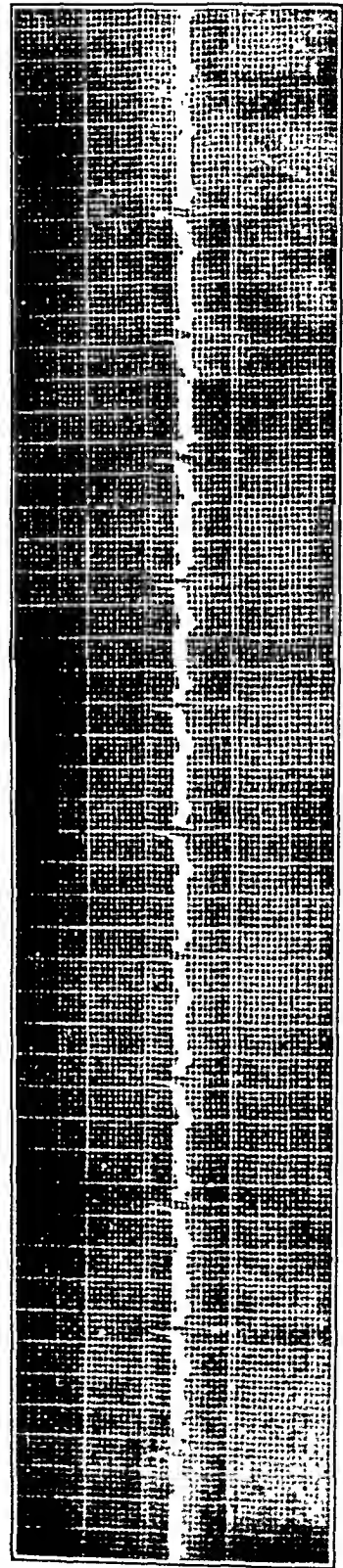


FIG. 3 (Case I).—Electrocardiogram taken in June, 1921, showing normal rhythm. Time in twenty-fifths of a second.



ing of dyspnea, cough, swelling (of feet, legs and abdomen), continuing for three weeks, with gradual onset. In her past life she had had rheumatic fever in 1914 and reported no other infectious diseases. Her family history was negative. The essential physical findings, upon the examination, were as follows: Orthopnea, many carious teeth, marked pyorrhea. Lung bed showed fluid at the right base. Examination of heart: The apex was in the fifth space, 14 cm. from the median line; rate regular, 148 per minute; no murmurs or accentuations audible. Blood-pressure: systolic, 180; diastolic, 100. Laboratory findings were negative except for a trace of albumin in her urine. Wassermann was negative. Electrocardiogram taken on admission showed auricular flutter; auricular rate, 300; ventricular, 150 (Fig. 1). The patient was put on large doses of digitalis. In two weeks her pulse-rate came down to 60, when digitalis was discontinued. An electrocardiogram taken on December 2, when the patient was up and about, showed an auricular rate of 300, with the ventricle responding to every fourth auricular beat. Pressure applied to the left vagus caused the ventricle to respond to every eighth auricular beat and had no influence whatever on the fluttering auricle (Fig. 2). An electrocardiogram taken recently showed a normal rhythm (Fig. 3).

CASE II.—C. D., age sixty-two years, shipping clerk, was admitted to the hospital April 7, 1920, and discharged May 3, same year, improved. On admission he complained of dyspnea, cough and palpitation for the four weeks preceding. His past history was negative except for multiple alveolar abscesses, causing him to have all teeth removed. The family history was negative. Physical examination showed a poorly nourished male, presenting cyanosis and dyspnea. The lungs showed many rales at both bases. Heart: The apex in fifth interspace, 11 cm. from median line; palpation of precordium was negative; the sounds were of poor muscular quality, suggesting fetal heart sounds; rate regular, 90 per minute. Blood-pressure, 110/75. Laboratory findings were negative. Wassermann reaction negative. The electrocardiogram taken on admission showed auricular flutter; auricular rate, 300 ventricular, 90 (Fig. 4). The patient received large doses of digitalis during his stay in the hospital. His auricular rate did not vary, but the ventricle, responding to the digitalis, slowed down to as low as 60. At this time the patient was discharged improved, and referred to the Cardiac Clinic, where he continued to receive digitalis in large doses. On May 11, because of a large pulse deficit being noted, an electrocardiogram was taken which showed auricular fibrillation (Fig. 5). On May 17 he became normal in rhythm and has remained so to the present time (Fig. 6).

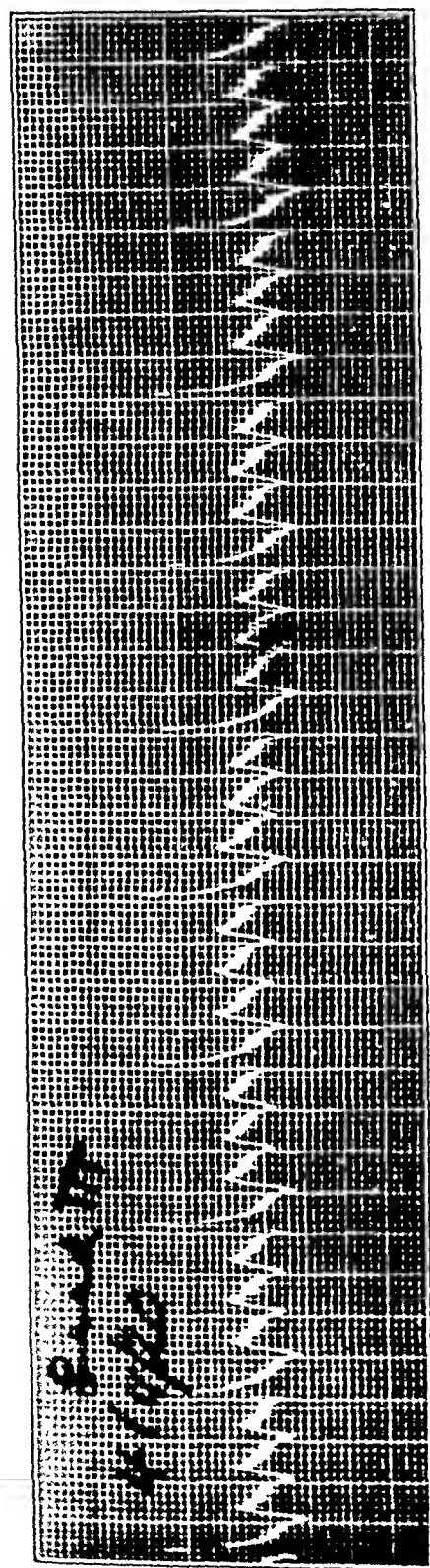


FIG. 4 (Case II).—Electrocardiogram taken April 4, 1920, showing flutter. Auricular rate 300. Ventricular 90. Time in twenty-fifths of a second.

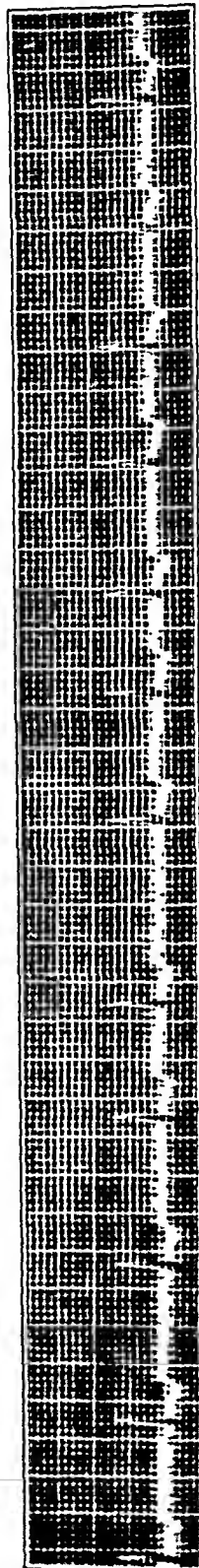


FIG. 5 (Case II).—Curve of the same patient taken May 11, 1920, showing auricular fibrillation following administration of large doses of digitalis. Time in twenty-fifths of a second.

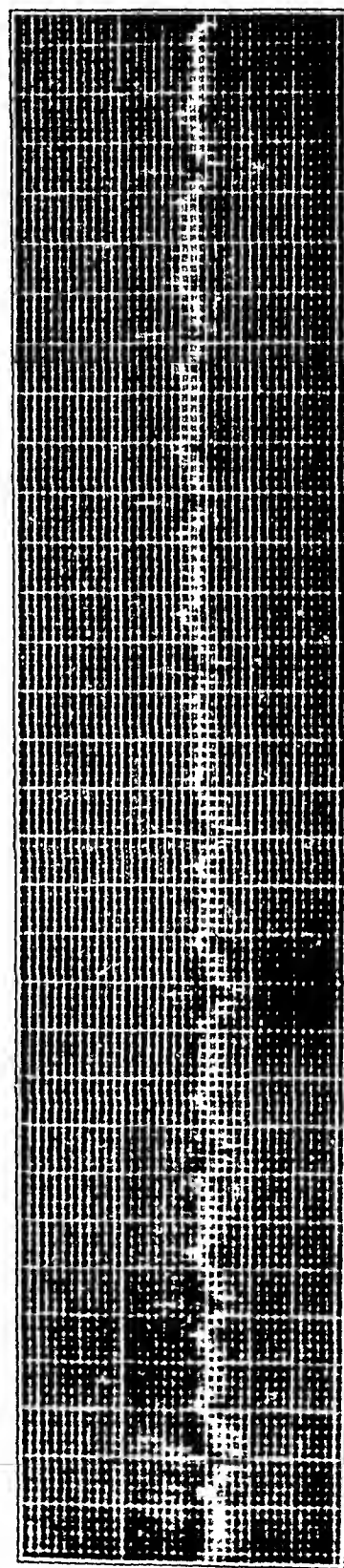


FIG. 6 (Case II).—Electrocardiogram taken May 17, 1921, showing normal rhythm. Time in twenty-fifths of a second.

CASE III.—A. K., aged fifty-eight years, dressmaker, was first admitted to the hospital in July, 1919, and discharged in September, 1919. On admission she complained of dyspnea, precordial pain, cough and attacks of syncope beginning three months prior to admission, the symptoms coming on gradually. In the past she had had measles, scarlet fever, rheumatism as a child, and influenza-pneumonia eight months prior to admission. Family history was negative. Essential physical findings at time of admission showed an elderly woman presenting poor muscular and bony development. The patient was orthopneic. Oral hygiene was markedly neglected and the teeth showed many cavities. The lung presented many moist rales at both bases. The heart: Apex in sixth space, 15 cm. from median line; rate, 90—regular; sounds of poor quality; no murmurs or accentuations audible. Liver 7 cm. below costal margin. Edema of both legs. Blood-pressure, 130/90. Urine examination was negative. Phthalein, 71 per cent at end of two hours. Wassermann reaction negative. Electrocardiogram taken on day of admission showed flutter; auricular rate, 270; ventricular, 90 (Fig. 7). The patient was put on large doses of digitalis, which caused the ventricular rate to fall as low as 44, but producing no effect whatever on the auricular rate. She was discharged, improved, on September 9; her auricle was still fluttering, but the ventricle had slowed down to about 70. The patient was readmitted October 21, 1919, with similar symptoms as when first entering the hospital, and died December 22, 1919. Electrocardiograms to the number of fifteen were taken, and all showed auricular flutter, despite the fact that she was being given huge doses of digitalis. Pressure upon the left vagus caused the ventricle to slow down but had no effect upon the auricle. Figs. 8 and 9 demonstrate the effect of pressure on the left vagus in this case, the auricle beating 14 times to 1 ventricular contraction in Fig. 8 and 22 times to 1 in Fig. 9.

CASE IV.—L. B., aged thirty-eight years, nurse by occupation, entered the hospital complaining of dyspnea, palpitation, feeling of oppression over the precordium and a sense of suffocation for three days prior to admission. She was admitted on December 15, 1920, and discharged March 6, 1921. Her family history was negative. In her past life she had had many severe infections up to the age of twelve, but since then had never been ill until admission. On physical examination she showed good muscular development and nutrition, with moderate amount of dyspnea. Teeth were in good condition. Tonsils small. Heart: Apex in fifth interspace, 8 cm. from median line; heart sounds of poor muscular quality; rate 90, regular; no murmurs audible. Blood-pressure, 130/80. Wassermann reaction negative. All laboratory tests, including those for hyperthyroidism, were negative.

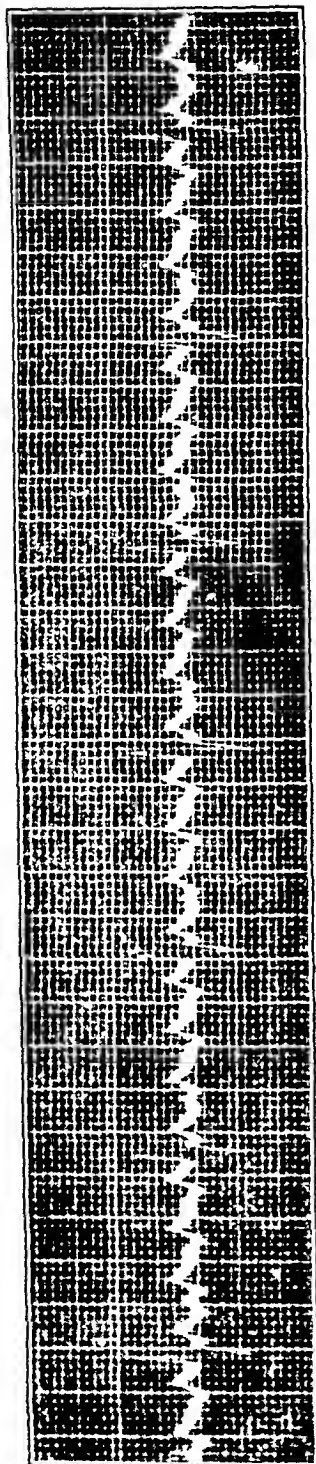


FIG. 7 (Case III).—Electrocardiogram taken on admission July, 1919, shows auricular flutter  $A = 270$ .  $V = 90$ . Time in twenty-fifths of a second.

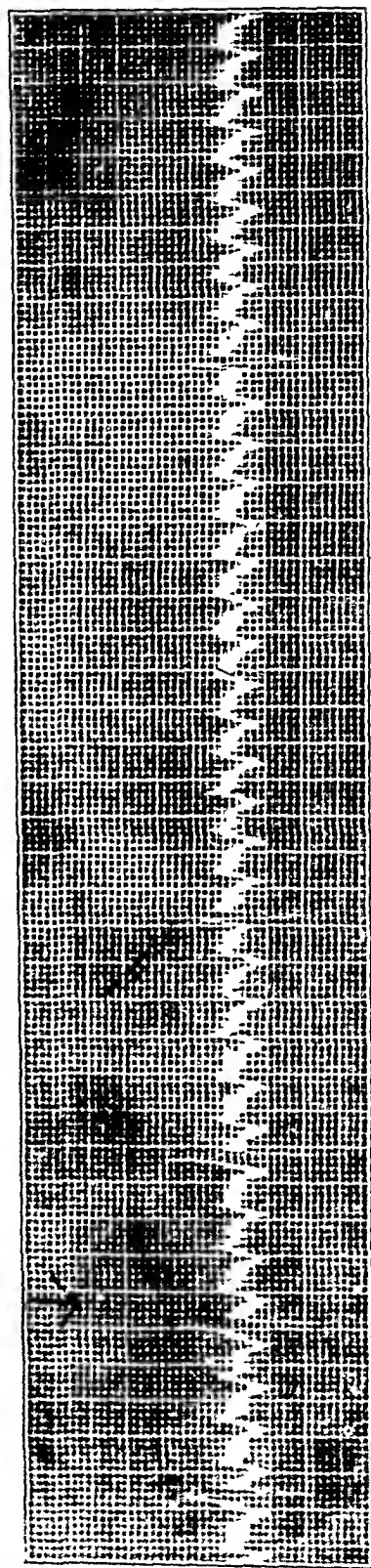


FIG. 8 (Case III).—Curve of the same patient showing the effect of left vagus pressure. Ventricle slowed down from 1:4 to 1:14. Time in twenty-fifths of a second.

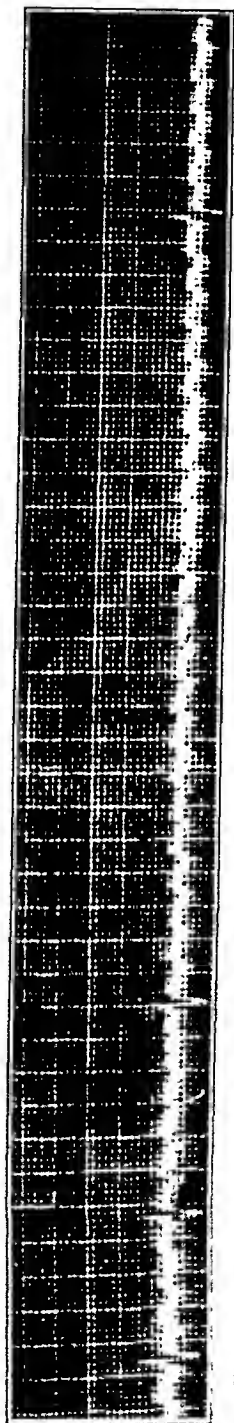


FIG. 9 (Case III).—Curve of the same patient showing the effect of left vagus pressure. Ventricle slowed down from 1:3 to 1:22. Time in twenty-fifths of a second.

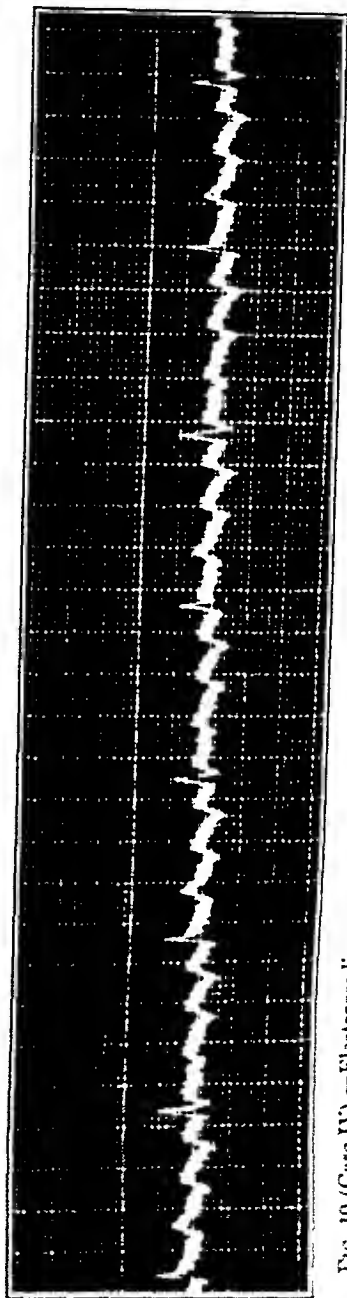


FIG. 10 (Case IV).—Electrocardiogram taken on admission December, 1920, shows flutter. This patient shows flutter up to the present time. Rate  $\Lambda = 300$ .  $V = 90$ . Time in twenty-fifths of a second.

Electrocardiogram showed auricular flutter; auricular rate, 300; ventricular, 90 (Fig. 10). The patient was put through an intensive course of digitalis therapy for thirty days, with a view to causing the heart to fibrillate, or, if this were not possible, of causing the ventricle to diminish its speed. The digitalis had no effect on the fluttering auricle, as was shown by the electrocardiograms taken at frequent intervals, but caused a slowing of the ventricle. When the ventricular rate fell below 60 digitalis was discontinued, in anticipation of auricular fibrillation. Unfortunately this did not take place, and the patient was put on atropine for a period of fourteen days, during which time the ventricular rate rose to 80, the auricular remaining the same. Exercise, emotion, even change of posture at times, caused an increase of the ventricular rate, but the fluttering auricle was uninfluenced throughout her entire stay in the hospital.

An electrocardiogram taken August 3, 1921, shows auricular flutter; auricular rate, 300; ventricular, 88. The patient is up and about and feels little discomfort.

CASE V.—St. H., aged fifty years, milliner by occupation, was admitted to the hospital January 27, 1921, complaining of sudden attacks of collapse with momentary unconsciousness during the last four years, with gradual onset. Dyspnea for the same period. Her family and past history, as far as could be ascertained, were negative. Physical examination showed the following essential points. The patient was a poorly developed, poorly nourished woman, presenting a moderate amount of dyspnea; teeth were noted to be in poor condition. Heart: Apex impulse in fifth interspace, 9 cm. from median line; rate 140, regular; no murmurs or accentuations audible; second aortic sound equals second pulmonic; peripheral arteries showed a moderate sclerosis. Laboratory findings were entirely negative. Electrocardiogram taken on admission showed a simple tachycardia. After a week's stay in the hospital the tachycardia changed to auricular flutter, with complete heart-block (Fig. 11). All electrocardiograms excepting two have shown auricular flutter; auricular rate, 360; ventricular rate, 30, and complete heart-block. At one time the patient showed complete heart-block with normal auricular rate: A rate is 90, V rate is 30 (Fig. 12). In this case the auricular sounds were distinctly audible when the auricles were fluttering, as described more fully under *Physical Signs*, below.

Electrocardiograms taken recently (Figs. 12a, 12b, 12c) show an impure flutter, with a transition to fibrillation in all three leads and numerous ventricular extrasystoles. These electrocardiograms demonstrate clearly the close association between auricular flutter and auricular fibrillation. The immediate passage of one into the other is clearly shown.

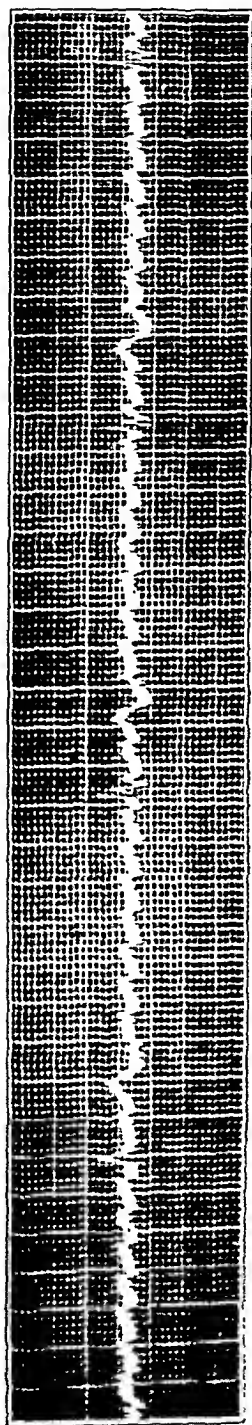


FIG. 11 (Case V).—Electrocardiogram showing auricular flutter (auricular rate 360) with complete heart-block. Ventricular rate 30. Auricular rate unusually high. Time in twenty-fifths of a second.

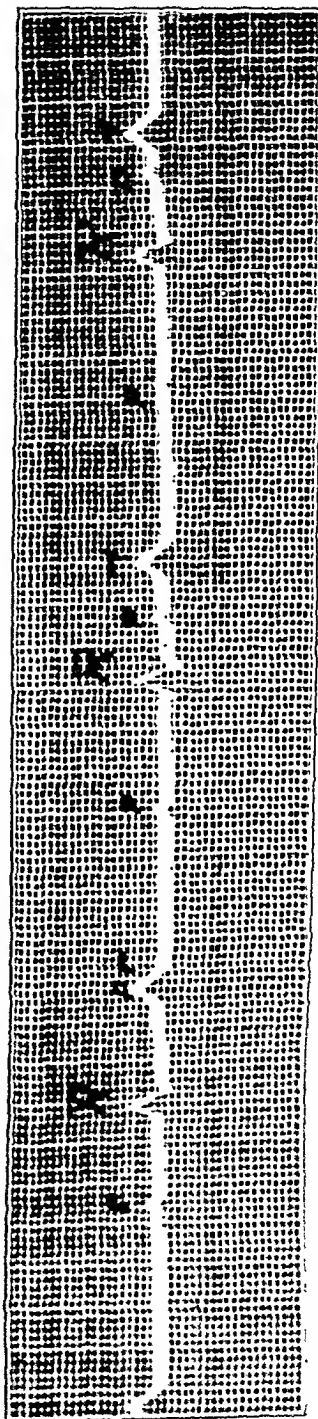


FIG. 12 (Case V).—Curve of the same patient showing complete heart-block. Auricular rate normal. Ventricle beating at its own intrinsic rate of 30. Time in twenty-fifths of a second.



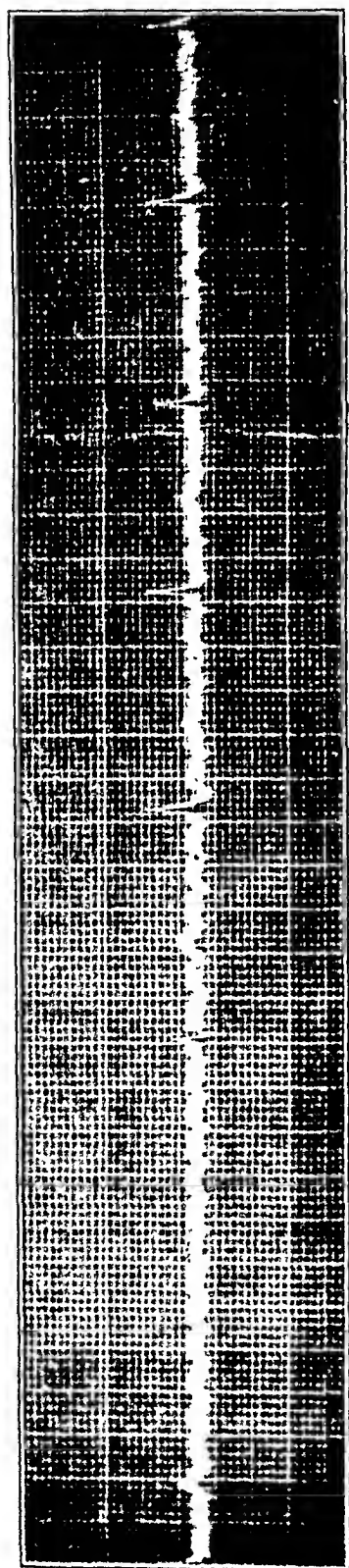


FIG. 12 A (Case V).—Lead I Electrocardiogram taken recently showing impure flutter with transition to fibrillation and many premature ventricular beats.

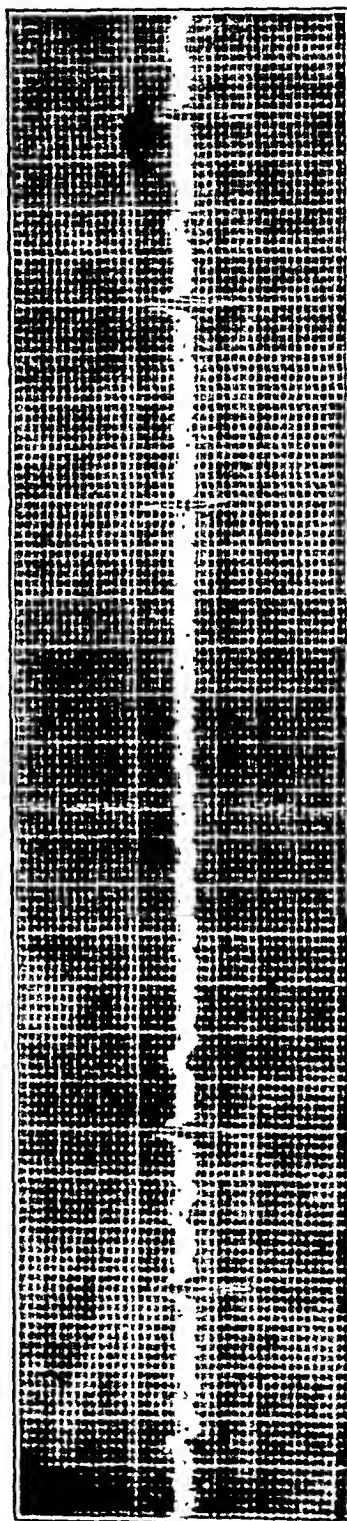


FIG. 12 B (Case V).—Lead II showing the same conditions as Lead I.



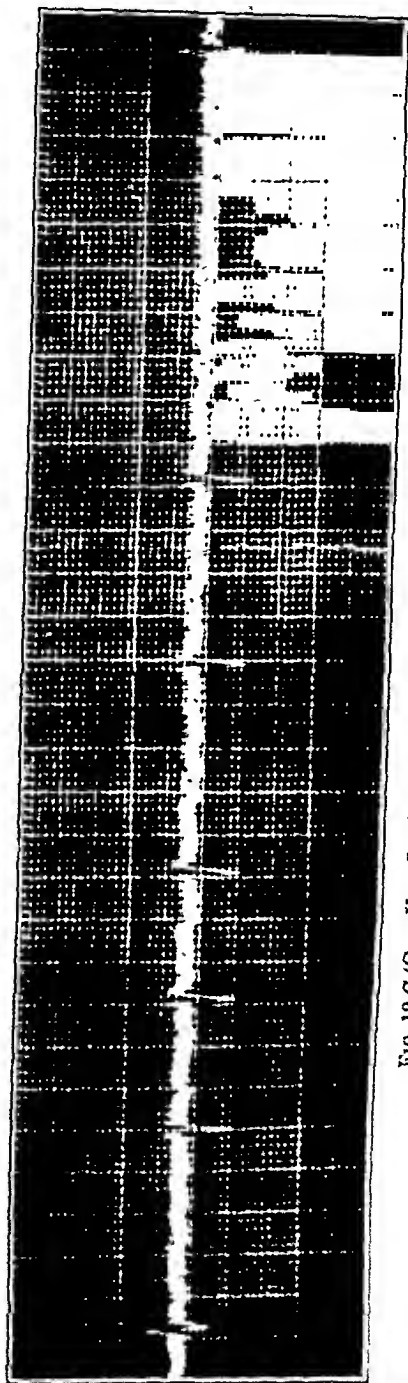


FIG. 12 C (Case V).—Lead III showing the same changes as Leads I and II.

CASE VI.—McK., aged thirty-three years, houseworker by occupation, was admitted to the hospital December 4, 1919, complaining of dyspnea, palpitation, sweating and enlargement of

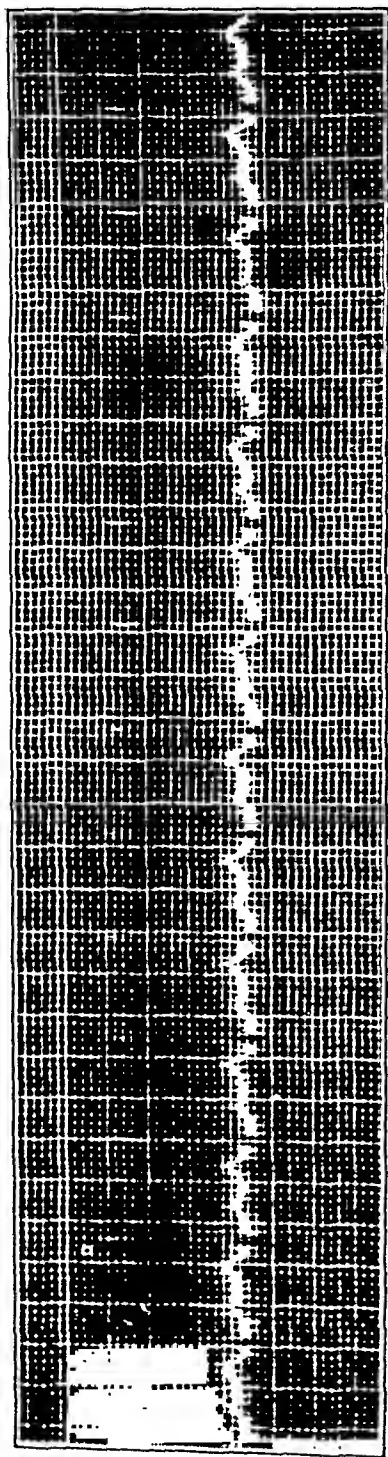


FIG. 13 (Case VI).—Curve taken December, 1919, showing simple tachycardia.

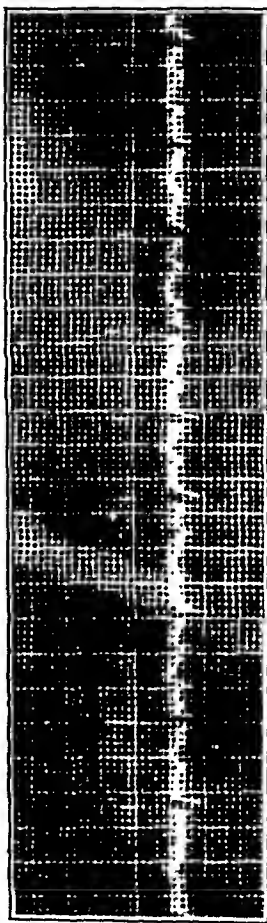


FIG. 14 (Case VI).—Same case showing auricular flutter.  $A = 270$ .  $V = 120$ . Time in twenty-fifths of a second.

her neck for five months prior to admission. Her family and personal history were entirely negative. On physical examination she showed moderate exophthalmos, fine tremor and moist skin. Tonsils were found to be hypertrophied and inflamed. There was a symmetrical bilateral enlargement of the thyroid gland, with bruit. Heart: Apex in fifth interspace,  $9\frac{1}{2}$  cm. from median line; rate, 130, regular; no murmurs audible. Blood-pressure, 128/85. Laboratory findings: The blood picture showed the mononucleosis of hyperthyroidism; Wassermann reaction negative, the remaining laboratory tests confirmed the diagnosis of hyperthyroidism. The patient had three applications of radium, on December 7, 13 and 26 respectively. Dose, 120 mg.; exposure four hours. Electrocardiographic study of this patient was very interesting, inasmuch as it demonstrated the rapid passage of one arrhythmia into another. The electrocardiograms showed the following transitions in the order named: Simple tachycardia rate 120 (Fig. 13); partial block; auricular fibrillation; normal rhythm; auricular flutter: A rate is 270; V rate is 120 (Fig. 14); and auricular fibrillation. On January 21, 1920, the patient developed pneumonia and died eight days later. Necropsy showed acute pericarditis and endocarditis, with lobar consolidation of both lower lobes of the lungs.

CASE VII.—M. R., aged forty-two years, housewife, entered the hospital December 2, 1919; complained of dyspnea, palpitation, nervousness, weakness, precordial pain, frequent nose-bleeds, all during the three months prior to admission. Her family history was negative. In the past she had some of the childhood diseases but no other infections. In 1909, or ten years prior to admission, she had experienced symptoms similar to the present ones, and in 1910 partial thyroidectomy had been performed, since which time she had been entirely well, until about five months prior to admission. On physical examination moderate exophthalmos, enlargement of the right lobe of the thyroid gland and fine tremor were found present. Heart: Apex in fifth interspace, 10 cm. from median line, sounds rapid, regular, rate 120; blowing, systolic murmur at base and apex, second aortic sound accentuated; no shocks or thrills. Laboratory findings confirmed the diagnosis of hyperthyroidism. Wassermann reaction was negative. The patient had five exposures of radium of four hours' duration each. Dose, 120 mg. Electrocardiographic study showed the patient going through the stages of tachycardia, of hyperthyroidism, auricular flutter, auricular fibrillation. Rate of flutter, A rate is 300, V rate is 120. This was demonstrated on one occasion only.

CASE VIII.—S. C., aged sixty-six years, governess, entered the hospital May 6, 1921, complaining of dyspnea and palpitation

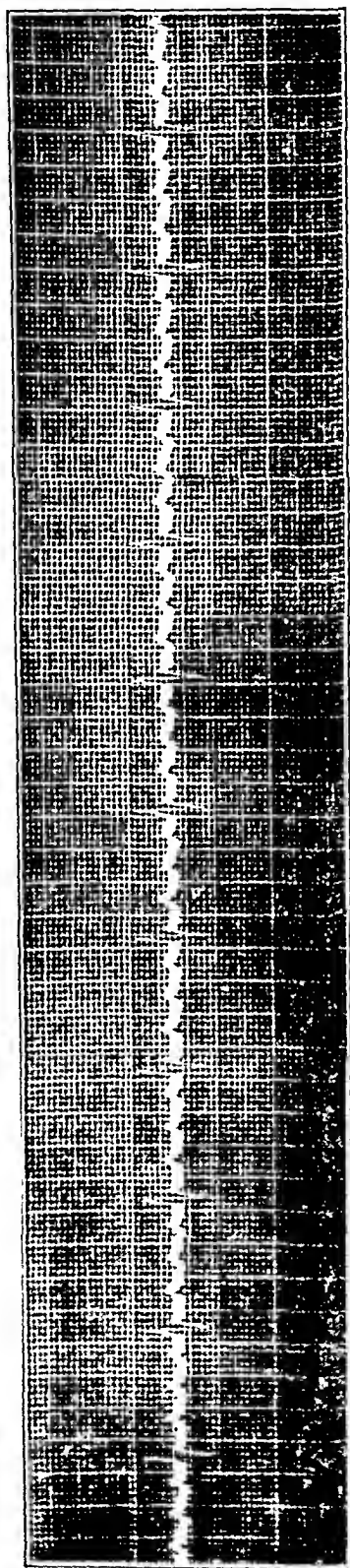


FIG. 15 (Case VIII).—Curve taken June, 1921, showing auricular flutter.  $A = 300$ .  $V = 90$ . Time in twenty-fifths of a second.

on exertion for one and a half years past. Had been taking tincture of digitalis for six months prior to admission, without improvement. During her past life she had suffered from frequent attacks of tonsillitis. Physical examination showed an obese woman, orthopneic; tonsils and teeth were negative. Heart: Apex in fifth interspace, 10 cm. from median line; rate 144, regular; no murmurs, shocks or thrills. Blood-pressure 185/125. Laboratory tests: Blood-picture of secondary anemia; Wassermann negative; urine, faint trace of albumin, with many granular casts; Phthalein 16 per cent at end of two hours; urea nitrogen in blood 26.4 mg.; blood sugar, 222 mg. The patient is still in the hospital. The first electrocardiogram showed an impure flutter. One week later this changed to a typical flutter, with an auricular rate of 300 and a ventricular rate of 90 (Fig. 15). Digitalis had no effect and quinidine sulphate has been tried without effect.

**Definition.** Auricular flutter is a condition characterized by rapid, regular and coördinated action of the auricles, in which the latter attain a speed so great that the ventricles are unable, or rarely able, to respond to each auricular impulse and thence a partial, or at times a complete block, is set up. The impulses no longer arise from the sinoauricular node, but from some other portion of the auricle.

As to what is the method of stimulation which in man leads to flutter and its coördinated states, this is as yet undetermined.

**Pathology.** Pathology of these cases is variable, as can be noted from the case reports presented above. Usually one of the following conditions is found to be present: old-standing disease of the vascular system or of the cardiac muscle; acute or chronic inflammation of the endocardium or of the myocardium, usually of infectious origin, such as lues, rheumatic fever, influenza and the like; infections of the pericardium and disease of the conducting system of the heart (also usually of infectious origin) coexistent with and spreading from endocardial or pericardial infection. Cases I and III in our series followed attacks of acute rheumatic fever, with definite cardiac involvement. Cases VI and VII gave a history of hyperthyroidism and were suffering with that condition on admission. Case V was definitely arteriosclerotic, with no history of infection. Case VIII was a cardionephritic, with history of frequent tonsillitis. Case II had a definite myocarditis on admission with no other history of infections than multiple alveolar abscesses. Case IV had no history of infection in the immediate past but had had many severe infectious diseases when a child.

**Symptoms.** The symptoms of auricular flutter are those of cardiac insufficiency of varying degree. The cardinal symptom, is that of dyspnea, all of our histories showing it to be the chief complaint. The shortness of breath is usually accompanied by

a sense of oppression and a feeling of suffocation and impending death. Most of the patients are conscious of palpitation of the heart, more especially so, those in whom the ventricle responds to every second beat. In some cases, particularly those in which a carditis has previously existed, owing to the gradual development of myocardial insufficiency, the output of the heart decreases and causes an impairment of cerebral circulation; a common complaint, therefore, is dizziness and faintness, especially so where there is a complete heart-block. Case V complained on admission of sudden attacks of collapse with momentary attacks of unconsciousness during a period of four years, a picture fairly typical of Stokes-Adams syndrome. The same symptoms were the principal ones also in Cases II, IV and V, in which no other pathology was noted clinically.

When other organic lesions are found the symptomatology is more complicated and must be correspondingly modified or enlarged.

**Physical Signs.** There may be none whatever; when the amount of cardiac insufficiency is slight (Case IV) and when the rate of the flutter may be 1 to 4 with a radial pulse of 80, none are likely to be noted. It then becomes impossible to make the diagnosis clinically. Most of the patients, however, present signs of endo- or myocardial insufficiency. In Case V of our series an additional interesting physical sign was noted on auscultation. This case, as stated in our case report, had at times auricular flutter with complete heart-block, the rate of the auricle being 360 and of the ventricle 30, which was its own intrinsic rate. On auscultation a very rapid tick-tack sound, resembling that of a fetal heart, was audible over the entire precordial area; it was heard best just inside the apex impulse. At the same time there could be heard the loud, muscular sound produced by the ventricular contraction, which occurred infrequently, approximately thirty times per minute. The auricular sounds in this Case V were very definite and were demonstrated to the students on several occasions. An interesting picture of flutter was shown by Hertz and Goodhart,<sup>4</sup> in 1908 upon the fluorescent screen, the auricular movements being distinctly visible.

**Diagnosis.** As may be readily appreciated, diagnosis of auricular flutter clinically, because of the few definite symptoms and physical signs pertaining to this condition alone, is exceedingly difficult. Before the introduction of the electrocardiogram the diagnosis was principally made on the jugular pulsation and the pulse-rate. The rapid pulsation of the jugular veins was diagnosed usually by visual observation, and occasionally by means of a polygraph tracing of the jugular pulsations and radial pulse. But, as generally admitted, jugular pulsations are of very questionable value,

<sup>4</sup> Quarterly Jour. Med., 1908-09, 2, 213.

especially in obese patients. The human eye is not trained to perceive the rapid vibration of the great veins at the base of the neck, particularly when the rate is between 200 and 300 per minute; consequently the diagnosis of auricular flutter was but very infrequently made. However, since the advent of the electrocardiograph the condition of auricular flutter has been found a very much more common one than at first supposed. It has frequently been stated, and often erroneously taught in our medical schools, that the diagnosis of auricular flutter should not be made unless the ventricular rate reaches at least 150. As a matter of fact the first case reported on the subject in the literature was of a man, aged sixty-one years, with an auricular rate of 273 and a ventricular rate of 34. This man was under observation for many years and showed this condition almost constantly; he suffered from frequent attacks of Stokes-Adams syndrome. In our own series a ventricular rate of over 100 was rare indeed, and notably in one case (V) which closely resembles Jolly and Ritchie's case,<sup>5</sup> the ventricular rate has been for long periods of time between 30 and 40. Of course, if the ventricle responded to every contraction, as in a case reported by McKenzie,<sup>6</sup> we would have a high ventricular rate; in that case the response of the ventricle was 280 to 300. However, this condition is extremely rare, and unless substantiated by electrocardiographic evidence it would incline us rather to consider it a case of paroxysmal tachycardia.

**Etiology.** As regards the etiology, Lewis<sup>7</sup> has recently advanced Mine's ingenious hypothesis to explain the origin and mode of propagation of the impulses producing flutter of the auricles. According to him, the rapid auricular contractions of flutter depend on an excitation wave in the auricle which travels continuously in a circular fashion around the openings of the great veins and spreads centrifugally with each flutter contraction throughout the entire portion of the auricle. To this fundamental condition he has applied the term "circus movement."

It will be of value to discuss, at this time, the relationships between paroxysmal tachycardia, auricular flutter, and auricular fibrillation, which are all closely allied and probably parts of the same pathological condition, as indicated by the frequency of the immediate transition of one into the other. A normal auricular contraction is initiated at the sinoauricular node and spreads in a definite direction throughout the entire auricular tissue. An abnormal impulse, causing a contraction of the auricle, originates in some region of the musculature other than the pace-maker, as demonstrated by an abnormal auricular complex in an electrocardiogram. Occasionally, small groups of premature auricular contractions may come close upon one another, giving rise to short parox-

<sup>5</sup> Loc. cit.

<sup>6</sup> Heart, 1920, 7, 293.

<sup>7</sup> Heart, 1910-11, 2, 317.

ysms of tachycardia. Usually they are ushered in by a shortened diastole and end with a compensatory pause.<sup>8</sup> Paroxysmal tachycardia and auricular flutter have ectopic pace-makers in the auricles, outside of the sinoauricular node; they are generally characterized by the same shortened diastole and compensatory pause, and are graphically shown when one is fortunate enough to get a record at the particular moment of the beginning of a flutter or paroxysm. The similarity of single or of groups of premature contractions, paroxysmal tachycardia, auricular flutter and auricular fibrillation can be shown further by the fact that the ectopic focus produces a complex different from the normal auricular P wave in the electrocardiogram. When the impulses again become initiated in the normal pace-maker the auricular complex becomes once more normal. It is an established fact, as pointed out by Lewis<sup>9</sup> and many other observers, that auricular flutter and fibrillation are closely allied.

In a theoretic generalization based upon our clinical report it seems to us that we would be justified in the assumption of an even closer relationship between the three conditions than has thus far been claimed in the literature. In auricular flutter there is but a single point of origin whence the excitation wave takes its course on its circus movement throughout the auricle; when flutter is established, the wave of excitation becomes independent of its point of origin. In auricular flutter the excitation wave consumed always the same period of time over the same stretches of auricular tissue.

It is our belief that the excitation wave follows the circus movement throughout the auricles in all three conditions. This wave of excitation travels regularly, covering the same distance in the same period of time, both in paroxysmal tachycardia and in pure flutter. In impure flutter and fibrillation the regularity of the excitation wave is interrupted in its passage through the auricular tissue, this interruption being more marked in fibrillation. In impure flutter the rhythm varies but slightly.

Our views are substantiated by experimental clinical work, which bears out the work of Lewis.<sup>10</sup> He believes that impure flutter differs from pure flutter in that there exists, in the former, an established local obstruction or actual barrier (block) which deflects the waves along new sinuous paths. In fibrillation the same condition of local barrier is present, only the barriers are multiple and involve most of the auricle. Whether the hypothesis of a single circular wave following a sinuous curve throughout the auricle holds true in auricular fibrillation, or whether there are multiple waves following circular paths through the auricle, we must con-

<sup>8</sup> Lewis, T.: *Clinical Electrocardiography*, p. 60 (Fig. 54).

<sup>9</sup> *Lancet*, *Loc. cit.*

<sup>10</sup> *Heart*, 1920 7, 127, 293.



fess ourselves, from our clinical observations, as still in doubt. There seems, however, no valid reason why there should not be, in auricular fibrillation, multiple points of origin with the excitation wave in the fibrillating auricle still following the circus movement; neither does there seem any reasonable objection to the hypothesis that two waves of excitation can travel in a circular fashion throughout the auricles, and we think that Lewis's theory fully explains the mode of propagation of impulses in the fibrillating auricle.

As a result of our observations we are inclined to the belief that auricular fibrillation and paroxysmal tachycardia are but forms of auricular flutter. It is known that in fibrillation the auricular rate is about 470 per minute, the ventricle responding irregularly, in no definite relation and ratio to the auricular movement; this results in a partial or impure block, almost identical with impure flutter. Drury and Ilescu,<sup>11</sup> by means of chest-leads, were able to eliminate the muscular interference and to obtain leads from the sagittal plane of the body. These chest-leads, taken as an ordinary lead 2 from a case of auricular fibrillation, showed coarse oscillations, about 470 per minute. The ordinary lead 2, taken at the same time, showed the usual type of irregular oscillations of the auricle obtained from limb leads. The limb leads seem to be unfavorable in demonstrating fibrillation, as it actually exists, in close relationship to flutter and paroxysmal tachycardia.

As taught up to the present time, auricular flutter, paroxysmal tachycardia and auricular fibrillation have been considered as separate and distinct from one another. In our opinion, they are one and the same condition, characterized merely by three different stages of varying degree and intensification. Theoretically it may be said that paroxysmal tachycardia is the first stage, flutter the second and fibrillation the third. We believe that all three manifestations can be fully explained by the theory of circus movement. As is frequently said, Nature never draws lines, and by means of the transitions which daily are presented in given cases by the electrocardiograph we are beginning to appreciate the closeness of the three conditions. The transition between auricular flutter and auricular fibrillation in the form of impure flutter is very well illustrated in our Case V.

In paroxysmal tachycardia the ventricle responds to every auricular impulse. Cases of auricular flutter, however, in which the ventricle responds to each impulse of the auricle are extremely rare; and for the simple reason, as we believe, that the ventricle cannot respond to every auricular impulse at so high a rate of speed for any length of time. Paroxysmal tachycardia, being of comparatively short duration, admits of the possibility of the ventricle maintaining an even gait with the auricle.

<sup>11</sup> Heart, 1921, 8, 171.

We consider the block in auricular flutter and auricular fibrillation as a protective measure on the part of Nature in order to maintain the cardiac tone at par as long as possible, and for the simple reason that in a great many cases the disturbance in rhythm appears to be purely functional. It is in the study of the transition from one condition to the other that the intimate relationship between the three becomes apparent. This extended and unbroken study was obviously impossible prior to the introduction of the electrocardiograph. In our series of cases 5 out of the 8 showed fibrillation at one time or another.

Cases of flutter experiments,<sup>12</sup> conducted to determine the effect of vagal stimulation, have led to the observation that large doses of atropin, although causing acceleration of the ventricle through vagus nerve palsy, have no effect on the auricular rate. This observation has been corroborated by the clinical facts brought out in the study of our series of 8 cases. Pressure on the vagus, as shown in Cases I and III (Figs. 2, 8 and 9) produces a marked slowing of the ventricle but does not influence the auricular rate. In Case III pressure on the left vagus altered the response of the ventricle from 3 to 1, to 21 to 1 (Fig. 9). Exercise, emotion and change of posture caused acceleration of the ventricle, but had a very slight effect, if any, on the fluttering auricle. Evidently the normal inhibitory action of the vagus, although still acting on the ventricle, did not influence the auricle.

Whether the etiology of auricular flutter lies in the lack of inhibition of the vagus on the auricle, stimulation of the sympathetic or accelerator being purely nervous, or whether the cause is in a pathologic change in the musculature of the auricle itself, is not definitely proven. Possibly both causes may contribute.

In all cases so far reported the age incidence does not seem to play any particular role. Cases have varied in ages from twenty-one to seventy-two; in our series the youngest was thirty-three and the oldest sixty-six. While auricular flutter may occur at almost any age the greatest number of cases represent middle life.

**Prognosis.** The prognosis of auricular flutter, as far as our series of cases can be said to lead to any conclusion, is problematical. It may be said, however, that the outlook in our series was modified by the complications which went along with each case. Case III died of kidney disease, Case VIII of pneumonia. In pure auricular flutter without any other complications the prognosis seems to be more favorable. The rhythm may return to normal, as in our Cases I and II (Figs. 3 and 6), or the heart may continue to flutter for years without any serious symptoms or discomfort to the patient. In the presence of other complications the lowered efficiency of the heart muscle in flutter, due to the very rapid con-

<sup>12</sup> Hertz and Goodhart: *Quarterly Jour. Med.*, 1908-09, 2, 213.

traction over a long period of time with an extremely shortened diastole, has a serious aspect. Cases of auricular flutter with complete heart-block, accompanied by syncopal attacks, present an uncertain future.

**Treatment.** When the case first comes under observation the patient should be put at rest in bed until his cardiac reserve has been increased. Digitalis is a drug of great value in this condition. Large doses, preferably in the tablet form, or intravenously, should be administered, with a view to causing the auricle to fibrillate. If this is accomplished the digitalis should be discontinued. Usually the auricle will then become normal. Unfortunately in some cases digitalis does not produce any effect on the heart other than slowing the ventricle, even when huge doses are administered. When digitalis fails to produce the desired effect the patient should lead a sedentary and uneventful life, to maintain the cardiac reserve at par. In all cases where possible electrocardiograms should be taken at stated intervals in order to judge the effect of the digitalis.

From the results obtained by us with quinidin sulphate we cannot at present draw any definite conclusions, as we used it in a few cases only.

**Summary.** 1. Auricular flutter is a condition characterized by rapid, regular and coördinated action of the auricle, in which the latter attains a speed so great that the ventricle is unable, or rarely is able, to respond to each auricular impulse, and thus a partial or a complete block is set up.

2. The symptoms depend upon the amount of the cardiac insufficiency and the presence or absence of complications, which will modify them. Dyspnea accompanied by palpitation and precordial distress are the predominant symptoms. In the presence of complications the symptoms will depend on the pathology.

3. The diagnosis of auricular flutter can in some cases be made with a sphygmograph tracing of the large veins and the radial pulse; but it is frequently unsatisfactory and sometimes impossible. Observation and auscultation of the patient is of little use in diagnosis of this condition. It can be definitely established only by the use of the electrocardiograph.

4. Our clinical experience bears out the experimental work. We believe that paroxysmal tachycardia, flutter and fibrillation are stages of the same pathologic condition causing cardiac insufficiency. We deem paroxysmal tachycardia to be the first stage, flutter the second and fibrillation the third.

5. Eight cases in all are here reported. In comparing them the most essential findings can be summarized as follows: In all our cases the auricle showed a remarkable stability while fluttering. Atropin, rest, exercise or emotion, while affecting the ventricle, had no effect whatever on the auricular rate. Five

of the cases of our series were associated at one time or another with other forms of arrhythmia.

6. As regards treatment, rest and digitalis restore many to normal rhythm. The use of quinidin sulphate is still in the experimental stage. Some few patients are not influenced by treatment, and the condition persists for years.

---

## CONCERNING THE WASSERMANN TEST IN ITS RELATION TO PRENATAL AND CONGENITAL SYPHILIS.

BY ROBERT A. KILDUFFE, M.D.,

DIRECTOR, LABORATORIES, PITTSBURGH HOSPITAL; DIRECTOR, LABORATORIES,  
MC KEESPORT HOSPITAL; SEROLOGIST, PROVIDENCE HOSPITAL.

(From the Laboratories of the Pittsburgh Hospital.)

THE student of medical history, and even the casual observer, cannot fail to be impressed with the fact that it moves, as it were, in cycles.

In the early days it might be said that the efforts of the physician were focussed, to a greater or less extent, upon the description and classification of the signs and symptoms whereby disease might be recognized. Following this might be said to have come the epoch of therapeutic endeavor directed toward the elaboration of methods of treatment; while the present age is avowedly that of preventive medicine, its aim and object being to forestall, anticipate and prevent the occurrence of disease in general in so far as this may be attainable.

It is inevitable that with such an end in view attention should be attracted and, to a large degree, focussed upon syphilis as one of the most generally distributed and far-flung infections to which the human race is subject; and of all the ramifications of this disease there is none of greater importance nor demanding more study than that which concerns itself with the prenatal and congenital phases of syphilis.

It is also inevitable that no consideration of the incidence of syphilis can be undertaken without a discussion as to the value and applicability of the Wassermann test as a means of diagnosis.

The introduction of the complement-fixation reaction as a means of diagnosis was undoubtedly a most valuable contribution to the elucidation of the study and treatment of syphilis, but like many other methods of laboratory investigation its usefulness can be enhanced or nullified in accordance with the skill with which it is employed and the acumen exhibited in its interpretation.

It is obviously essential that the complexities and niceties of

technic inherent in the reaction should be thoroughly and intelligently comprehended by those applying it; and it is equally, and perhaps even more, essential that a full and complete understanding of its limitations should be had by those charged with its interpretation, for, after all, the value of any method of examination, clinical or laboratory, rests mainly upon its interpretation in connection with and in terms of the particular patient.

Schleiter<sup>1</sup> emphasizes this when he calls attention to a prevalent tendency "to order a number of investigations by the laboratory, which may often be unequalled for, in the expectation that they will, in some mysterious manner, whisper the correct diagnosis"; and reiterates the important and, it would seem, obvious fact that "the physician owes it to himself to have a clear understanding of the laboratory procedures he calls to his aid—their principles, sources of error and when they are are not applicable to a given case."

In no procedure are these requirements of more importance than in the clinical application and interpretation of the Wassermann test, and in few instances are more care and skill required in the proper evaluation of the results obtained than when it is used as a means for the detection of prenatal syphilis.

The importance of syphilis as a cause of fetal death and of the pathologic sequences following birth is well known and often commented upon.

A most careful, extensive and masterly study of the value of the Wassermann reaction in obstetrics as a means to the diagnosis of prenatal syphilis is that of Williams,<sup>2</sup> which brings out the fact that 26 per cent of all fetal deaths between the end of the seventh month of pregnancy and the first two weeks following delivery are due to syphilis.

These statistics agree with those of other observers and are corroborative and illustrative of the widespread incidence of this disease and furnish a sufficient reason for the present concentration of attention upon it by all who are interested in preventive medicine.

Obviously the first step toward the prevention of any disease is its detection and the subsequent handling of the sufferer in such a fashion that he shall not furnish a source from which it may be transferred to others, and there are a few instances in which this is of greater importance and more promising of ultimate success than in the problem presented by prenatal and congenital syphilis. Competent observers have shown that if the presence of early syphilis is recognized a large proportion of infants otherwise doomed to the evils of inherited syphilis can be brought into the world free of infection; or, certainly, if this cannot be fully attained they

<sup>1</sup> Laboratory Diagnosis, *Pennsylvania Med. Jour.*, 1921, 25, 77.

<sup>2</sup> The Value of the Wassermann Reaction in Obstetrics Based upon a Study of 4547 Consecutive Cases, *Bull. Johns Hopkins Hosp.*, 1920, 21, 356.

can be so treated that their ultimate destiny as healthy citizens can be fulfilled.

Following the introduction of the Wassermann reaction, it was, naturally, largely depended upon to furnish the requisite diagnostic information. Unfortunately, as has been succinctly said:<sup>3</sup> "A product of our modern methods of diagnosis and treatment (of syphilis) is the pseudosyphilographer. To him the clinical study of syphilis is unnecessary. The public Wassermann laboratory makes the diagnosis without charge and a few injections of arsphenamin clear up the lesions." This, though a severe indictment, is too often true.

The Wassermann reaction as a routine method of investigation in obstetric cases is coming more and more into general use; the interpretation of the results obtained, however, for reasons not always easily explainable, presents in general a greater difficulty than in cases of acquired syphilis or of congenital syphilis investigated in later childhood.

A frequent method of utilizing the reaction in obstetrics is to apply the test to the cord blood, because this does not necessarily inform the patient of the nature of the investigation pursued and because the test is easily made without incurring the objections or refusal of the patient to submit to it.

The results of series collected, however, present great difficulties in the way of interpretation.

Williams<sup>4</sup> in 4000 mothers serologically examined obtained a positive Wassermann in 11.2 per cent, and draws the conclusion, from an analysis of the results obtained that a positive Wassermann on the part of the mother during pregnancy does not inevitably mean that the child will be syphilitic, as in only 57 of the 169 children concerned—all of Wassermann positive and untreated mothers—were clinical or anatomic evidences of syphilis elicited.

In Wassermanns made on the fetal blood at the time of birth, 38, or approximately 1 per cent, positives occurred; 29 of these cases were later investigated, some as late as three years after, with the following results: 17 developed definite evidence of syphilis; 5 showed no signs except a continued positive Wassermann; 7 showed no signs with a negative Wassermann.

A similar investigation of children whose Wassermann was negative at birth, however, showed 10 whose Wassermann was later positive, and he therefore states that "In view of these findings a positive Wassermann at birth does not imply that it will remain so, and, conversely, a negative Wassermann at birth does not necessarily mean that it may not become positive later." He therefore concludes that the information obtained by the

<sup>3</sup> Smith, C. M.: Treatment of Early Syphilis, Arch. Dermat. and Syph., 1921, 6, 723.

<sup>4</sup> See note 2.

Wassermann made upon the fetal blood at birth is not commensurate with the time and money employed in such an investigation.

It is, of course, to be recognized that even though the results of the Wassermann tests upon cord blood are apt to be at times fallacious and are always to be carefully and conservatively interpreted, still when taken in conjunction with the history and a careful examination, together with, if possible, an intelligent "follow-up" in a certain proportion of cases, information of definite value may be obtained, and in any serious effort toward the eradication of any disease no means of even slight promise should be neglected.

We have come to realize that the Wassermann test is not infallible, and it is unfortunate that so much emphasis has been placed upon it as to give rise to a distorted idea of its value. It should be unceasingly reiterated that the meaning of a Wassermann reaction depends very largely upon the particular technique and degree of care with which it has been performed, and, further, upon an equal care in its interpretation and correlation with the patient. In any case, where properly checked and controlled, a positive Wassermann may be taken as very strongly presumptive evidence of the presence of syphilitic "reagin" in the blood.

Of great importance is the fact brought out by Thaysen<sup>5</sup> that unaccountable variations in the strength and even in the occurrence of the Wassermann reaction may take place in untreated cases of known syphilis. This is illustrated in Williams's series by 3 cases in which Wassermann-positive mothers who gave birth to syphilitic children, though untreated, gave a negative Wassermann some weeks or months later. Until we know more about the mechanism and *modus operandi* of the reaction this phenomenon cannot be satisfactorily explained. If, as has been tentatively assumed, the substance or substances giving rise to the reaction are lipoidal and connected with the lipoid metabolism of the body it is a possible presumption that they might be present in varying amounts at varying times in accordance with the reaction of the body to the infection; or, again, a possible explanation may lie in the so-called "selective action" of the reacting body in the presence of a series of antigens of similar type, all of which, until a further understanding of the reaction is had, must be purely hypothetical.

The ideal method of investigation in obstetric cases would, of course, imply a serologic examination of the child, and of both parents as well as a repetition of the tests later when indicated in conjunction with a careful and painstaking history and examination. This, of course, is rarely feasible.

Williams also emphasizes the importance of a routine microscopic examination of the placenta for the so-called Fränkel's disease,

<sup>5</sup> Spontaneous Variations in the Strength of the Wassermann Reaction, *Acta Med. Scandinav.*, 1921, 55, 281.

upon the presence of which he places great reliance as an evidence of syphilitic infection.

It seems not untimely to mention here what should be obvious, and yet what, in these days of laboratory tests galore, is sometimes overlooked—the exceeding value of a careful, keenly taken history, the importance of which in the diagnosis of syphilis is well emphasized by Broeman.<sup>6</sup>

The complete cycle of the ideal examination outlined above is, unfortunately, infrequently possible, but that some investigation should undoubtedly be made is indisputable, and the most feasible in the long run is the routine examination of the fetal blood with a full realization of the inherent fallacies of the method.

That such a method is not entirely without value is evidenced by the literature. Campbell<sup>7</sup> in a series of 34 latent cases reports 82.3 per cent of positive reactions.

Jeans and Cooke,<sup>8</sup> correlating the results of cord Wassermanns and placental studies with the results of Wassermanns made from six to nine months later, found a correspondence of 63.3 per cent of cord Wassermanns as compared to 27 per cent of placental examinations.

Ross and Wright<sup>9</sup> note the fact that congenitally syphilitic babies tend to give a negative Wassermann until a month or so after birth, and state that whether a positive Wassermann reaction with the cord blood is indicative of syphilis in the mother and *not* in the child, as believed by Fildes, or in the mother *and* the child, as held by Kolmer, the occurrence of 3.5 per cent of positives independently obtained by two observers is highly suggestive and warrants the use of the method.

Fordyce and Rosen<sup>10</sup> agree with Williams as to the inexpediency of cord Wassermanns and call attention to the fact that syphilitic babies, positive at birth, may later be negative and, still later, again positive. They feel, also, that a cholesterin plus only Wassermann in the mother before delivery requires corroboration, and state that in their experiences this type of reaction may occur in normal women during pregnancy.

Kolmer<sup>11 12</sup> believes that the Wassermann on the cord blood

<sup>6</sup> A Thorough History an Important Factor in Syphilis, *Am. Jour. Syph.*, 1921, 5, 565.

<sup>7</sup> Pathologic and Public Health Aspects of the Diagnosis of Syphilis, Acquired and Congenital, in the First Year of the Disease, *Public Health*, London, 1921, 7, 13.

<sup>8</sup> The Incidence of Hereditary Syphilis, *Am. Jour. Dis. Children*, 1921, 22, 402.

<sup>9</sup> The Incidence of Congenital Syphilis among the Newly Born, *Lancet*, London, 1921, 1, 321.

<sup>10</sup> Treatment of Antenatal and Congenital Syphilis, *Arch. Dermat. and Syph.*, 1922, 5, 1.

<sup>11</sup> Prenatal Syphilis with a Plea for its Study and Prevention, *Am. Jour. Dis. Children*, 1920, 19, 344.

<sup>12</sup> Immunity to Syphilis, with Special Reference to Congenital or Prenatal Syphilis, *Arch. Pediat.*, 1920, 37, 129.



alone cannot be relied upon to always give complete information, and notes the value and applicability of the luetin test to the problem.

That there is a difference of opinion as to the expediency of the cord Wassermann is evident, but, at all events, if, as is frequently the case, this is the only avenue of investigation available, it seems questionable whether or not it should be entirely neglected.

This is the method which has been employed in the routine investigation of obstetric cases in the Pittsburgh Hospital in a series of 269 cases, and the results of the series, though too small to be of great value or significance, are reported on the principle that, as the Scotch say, "Many a mickle makes a muckle."

The method employed follows:

*Serums.* These were collected from the cord immediately after delivery; the serums were separated and inactivated for fifteen minutes at  $56^{\circ}$  C. immediately before the test. Practically all serums were tested within twenty-four hours of their collection and used in dose of 0.2 cc.

*Amboceptor.* Glycerinated amboceptor, diluted with normal salt solution according to titer, and used in a constant dose of 0.1 cc.

*Complement.* Diluted 1 to 10 with normal salt solution and titrated immediately preceding the main test in the presence of 0.1 cc of amboceptor and 0.5 cc of 2.5 per cent suspension of sheep cells.

*Antigen.* A triple battery was always used, consisting of cholesterinized (0.4 per cent) extract of the human heart, acetone insoluble lipoids of the human heart and alcoholic extract of syphilitic liver. The dose was always from five to ten times the antigenic amount, and this amount was always from five to twenty times less than the anticomplementary unit.

Preliminary incubation was for one hour in an ice-water bath at  $4^{\circ}$  to  $6^{\circ}$  C., after which the rack was placed in the  $38^{\circ}$  C. bath for five minutes, removed, amboceptor and sheep cells added and returned to the  $38^{\circ}$  C. bath for thirty minutes, or until all controls were hemolyzed.

The usual controls, including a known positive and negative, were always included.

This technic has been carefully checked and is believed to give reliable results.

In 269 cord bloods so tested there were 227 negative reactions and 28 anticomplementary serums.

There were fourteen cases in which a positive result was obtained, an incidence of 5.1 per cent.

In every case in which a positive reaction was obtained a Wassermann was made upon the mother and, whenever possible, upon the father, and an effort made to obtain any history of value in corroborating the test.

The results of the investigations are shown in the following table:

Cord blood Wassermann.●	Wassermann of mother.	Wassermann of father.	History and remarks.
1. C + <sup>4</sup> A + <sup>4</sup> S + <sup>2</sup>	Negative	Not obtained	None elicited.
2. + <sup>†</sup> . . . . .	....	Not obtained	Five miscarriages.
3. C + <sup>4</sup> A + <sup>4</sup> SO . . .	Negative	Not obtained	None elicited.
4. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
5. + <sup>4</sup> . . . . .	Negative	Negative	None elicited.
6. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
7. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
8. + <sup>4</sup> . . . . .	+ <sup>4</sup>	Negative	Spinal; colloidal gold 5555100000; patient has paresis.
9. + <sup>4</sup> . . . . .	Negative	Negative	None elicited.
10. + <sup>4</sup> . . . . .	Negative	Not obtained	One abortion; one still-birth.
11. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
12. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
13. + <sup>4</sup> . . . . .	Negative	Not obtained	None elicited.
14. + <sup>4</sup> . . . . .	Negative	Anticomplementary	One abortion.

C = cholesterinized extract; A = acetone insoluble lipoids; S = syphilitic liver extract.

† +<sup>4</sup> = plus 4 in all antigens.

For various reasons, mainly because most of the patients were private cases, no satisfactory "follow-up" was possible, and the possible results of serologic examinations, if made later, is purely speculative. Despite this fact, and regardless of the further fact that in many instances the history leaves much to be desired, data corroborative of the Wassermann were obtained in 3 of the 14 cases, or approximately 30 per cent, findings which would seem to warrant a continuance of the method.

**Conclusion.** These results, in a small way, are in agreement with those of more extensive investigations, and seem to warrant the conclusion that the results of cord Wassermanns are not to be unreservedly relied upon when taken alone, and should not be made the sole basis for a diagnosis of syphilis. If the subject of prenatal and congenital syphilis is to be the object of a concentrated attack, it is obvious that serologic investigations must be extended to include not only both parents but also the child at birth, and in later infancy when the results of Wassermann reactions are apt to be more truly indicative of the presence or absence of luetic infection.

## TWO INSTANCES OF DEFECTIVE INTERVENTRICULAR SEPTUM OF THE HEART.

BY H. W. CAREY, M.D.,

TROY, N. Y.

THE congenital anomalies of the human heart due to defective development are of many kinds and have been described by many observers. Some of them are rarely detected during life, either because no symptoms are produced by the defect or because the distinctive symptoms and signs are encountered so infrequently that they are not familiar to the clinician.

The two cases to be described have to do with defects in the interventricular septum, and although both were congenital, one produced no symptoms whatever and the other caused symptoms, signs that were supposed to be due to an open ductus Botalli.

In the sections devoted to congenital heart disease in Osler's *Modern Medicine*, volume IV, contributed by Abbott, defects in the interventricular septum were found in 161 of the 412 cases studied, and in 149 of these the defect was situated in the membranous portion and in 12 in the muscular portion of the septum. In the first case to be described here the defect was located at the base, but in the second case it was in the muscular portion of the septum. Since the publication of the article by Abbott<sup>1</sup> but one similar case can be found, the one reported by Meyer<sup>2</sup> in 1914.

CASE I.—C. B., female, aged twenty-three years, single.

*Family History.* Father alive and well. Mother dead, cause unknown. One brother died at seven years with heart disease, which began when he was one year old. He was cyanotic. Five other children died of pneumonia and croup.

*Past History.* Whooping-cough at the age of four years. No history of any other illness.

*Present Illness.* This began when she was six years old and continued until her death. The first sign noticed was cyanosis and the first symptom shortness of breath on exertion. Her condition became aggravated as time went on and the shortness of breath became so severe that she would often stagger and fall on the street. After a rest of a few minutes she would be able to proceed. The dyspnea finally became so acute that she entered the hospital, and while there she developed a fever due to sepsis, of which she died.

*Physical Examination.* The patient was short in stature and diminutive in size. The lips, finger-tips and ears were cyanotic

<sup>1</sup> Osler's *Modern Medicine*, 1908, 6, 355.

<sup>2</sup> *Jour. Anat. and Physiol.*, London, 1913-14, 48, 123-127.

and the cheeks had a mahogany flush. The fingers and toes were clubbed. After the slightest exertion there was dyspnea. There was no edema.

The heart, at the apex, had a diffuse impulse which could be felt 0.5 cm. to the left of the midclavicular line. A continuous thrill could be felt at the junction of the third costal cartilage and the sternum. By auscultation a murmur could be heard which continued through systole and diastole. It was heard best in the second left intercostal space and along the left border of the sternum to the apex. The pulse-rate was 80 and the rhythm regular.



FIG. 1.—Case I. Defect in the membranous portion of the interventricular septum, showing vegetations in one leaflet of the aortic valve.

The chest was poorly developed, the anteroposterior diameter diminished and there was retraction above and below the clavicles. The breath sounds were normal.

The liver was a trifle enlarged, the dullness extending from the fifth rib to 2 cm. below the costal margin, where the edge could be felt.

*Clinical Diagnosis.* Septic endocarditis. Probable patent ductus Botalli.

*Postmortem Examination.* The body of a slightly built woman, 5 feet 2 inches tall. There was a small amount of edema of the feet and legs. Marked cyanosis of the lips, face, hands and feet. The pupils were slightly dilated. There was no lymphatic enlargement.

The peritoneal cavity contained about 500 cc of dark-colored fluid. In all other respects the peritoneum and its contents were normal.

*The Heart.* The pericardium was free from adhesions and the fluid was excessive. The heart itself was enlarged and measured 13 x 12 x 7 cm. The enlargement was due to distention of the right auricle and hypertrophy of the right and left ventricles. The left auricle was small. When the chambers of the heart were opened the right ventricular wall was hypertrophied and equalled in thickness the wall of the left ventricle, while the wall of the right auricle was so hypertrophied that it equalled in thickness the ventricular walls. The mitral and tricuspid valves were normal. The orifice of the pulmonary artery was noticeably diminished in circumference and its valves thickened. On one cusp of the aortic valve there were extensive vegetations, in the smears and cultures of which the *Staphylococcus aureus* was found.

In the interventricular septum, just beneath one leaflet of the aortic valve, was an aperture 1.5 cm. in diameter, which opened on the right side just beneath the adjacent leaflet of the pulmonary artery. It was oval in shape and was bounded laterally and above by a thin membranous tissue and beneath by the cardiac muscle. On account of this defect there was an arteriovenous communication between the ventricles.

The lungs showed no abnormality except an old organized infarct on a posterior lower margin. The spleen was somewhat enlarged. It measured 15 x 7 x 5 cm. The pulp appeared congested and swollen. The uterus was infantile. The remainder of the examination revealed no abnormality and is omitted.

The microscopic examination of the tissues confirmed the gross findings.

*Diagnosis.* Congenital defect of the membranous portion of the interventricular septum. Acute vegetative endocarditis. Old infarct of the lung.

CASE II.—J. D., aged thirty-seven years. Complaints of nervousness and weakness, loss of appetite, sleeplessness and shortness of breath on exertion.

*Family History.* Unimportant.

*Past History.* Has had the usual diseases of childhood. No history of any venereal infection. Has drunk to excess and taken no care of himself at all.

*Present Illness.* Began two days ago with the symptoms described above. He is very nervous, unable to keep quiet. Keeps jumping out of bed and sees things at night. His speech is thick and there is a marked tremor of the hands. He is continually picking at the bedclothes.



FIG. 2.—Case II. Funnel-shaped depression in the muscle of the interventricular septum with an opening into the right ventricle at its upper margin.

*Physical Examination.* The face and body appear much congested. The tongue is coated and tremulous. The pupils are midwide and equal and react to light and accommodation. The throat is clear. In the lungs there are no rales or dulness. The vesicular resonance of the left lung is diminished on account of the enlargement of the heart.

The heart dulness is much increased to the left. There is no thrill. There is a rough systolic murmur at the apex which is transmitted to the back and heard at the angle of the scapula. The liver can be felt three inches below the costal margin. The edge is smooth.

The mental condition is clouded. The patient is delirious. The superficial and deep reflexes are exaggerated. The cranial nerves are intact. The remainder of the examination reveals no abnormalities.

*Diagnosis.* Delirium in potu. Mitral regurgitation.

*Postmortem Examination.* The subject is a fairly well-nourished man. The pupils are midwide and equal. The lips and mucous membranes are pale. There is no edema of the extremities.

The peritoneum and the organs within its cavity are normal except for a chronic obliterative appendicitis.

The heart is covered by a smooth pericardium in which there is no excess of pericardial fluid. It measures  $13 \times 9 \times 7$  cm. When opened, the left ventricular wall is 2 cm. in thickness; the right is not hypertrophied. The mitral leaflets are somewhat thickened and the valve incompetent.

The papillary muscle extending to one leaflet of the tricuspid valve is fused with the columnæ carneæ and has caused a shortening of the chordæ tendinæ, rendering the valve incompetent. This makes one leaflet short while the remaining two appear lengthened in comparison. In the interventricular septum on the left side there is a depression measuring  $4 \times 2$  cm. and 1 cm. in depth. There is a corresponding depression into the right ventricle. Near the upper margin of the depression, on the left side of the septum, there is an opening 4 mm. in diameter which communicates with the cavity of the right ventricle. The appearance is similar to a funnel pointing toward the right ventricle. On the left side the walls of the depression are composed of muscle, but on the right side there is dense fibrous tissue about the opening. No other abnormality of the heart is found.

The lungs are crepitant but present a congested appearance, particularly in the lower lobes, presumably due to hypostatic congestion. The right lung is adherent to the diaphragm.

The spleen measures  $20 \times 12 \times 4.5$  cm. It is firm in consistency, and on section the pulp appears increased in amount.

The liver is roughened by nodules on its surface, which vary in size from a pin-head to a pea. It has a mottled reddish color and its consistency is firm. On section it cuts with resistance and the connective tissue is distinctly increased. The remainder of the examination reveals no abnormalities.

*Microscopic Examination.* Microscopic examination of the tissue about the defect in the septum shows no evidence of any inflammatory reaction. Sections from the lung show the bronchi packed with polynuclear leukocytes and the alveoli filled with red blood cells, polynuclear leukocytes and blood serum. The sections from the spleen show a marked increase in the blood content of the pulp with a diminution in the size of the Malpighian bodies. The liver contains a great increase in the interlobular

connective tissue with compression of the lobules. The liver cells are fatty. In the interlobular connective tissue are many long vessels lined with low epithelium which are taken to be bile capillaries. These are frequently surrounded by large accumulations of lymphocytes.

*Diagnosis.* Tricuspid insufficiency due to obliteration of the papillary muscle, which is bound firmly to the ventricular wall.

Relative mitral insufficiency. Interventricular septum defect through funnel-shaped opening. Chronic passive congestion of the lungs and spleen. Early bronchopneumonia. Cirrhosis of the liver.

Several theories have been advanced in explanation of the defects in the interventricular septum. We know that the interventricular septum is not complete in early fetal life, the defect being situated along the upper margin. It is due to the failure of the septum to complete its development that explains defects like the one described in Case I. Stenosis of the pulmonary artery and transposition of the pulmonary artery and aorta are frequently found coexisting with the interventricular septum defect. In the case of these multiple anomalies opinion has been divided upon the question of which was the primary one.

Meckel believed that the defect in the septum was primary and that the diversion of blood through it led to a stenosis of the pulmonary artery from disuse. Hunter and Morgagni were of the opinion that pulmonary stenosis in fetal life was the primary cause; the increased pressure in the right ventricle produced by the stenosis prevented the septum from closing.

In the Hunterian Lectures of 1909, Keith was of the opinion that faulty fusion of the bulbus cordis and incomplete development of the infundibulum played an important role in explaining the congenital anomalies of the heart. A large number of the instances of pulmonary stenosis are due to incomplete expansion of the infundibulum after the bulbus cordis has fused with the right ventricle. In 80 to 90 per cent of the cases of pulmonary stenosis that Keith has seen there has also been a foramen in the interventricular septum. The interventricular septum closes under normal conditions in the second month of fetal life, and it is at this time that the infundibulum expands and opens up so that both the stenosis of the pulmonary artery and the incomplete closure of the septum might be due to incomplete development of the infundibulum. This theory of Keith's does not explain the septum defects that occur without any other coexisting anomaly.

The symptoms produced by defects in the interventricular septum depend a great deal on the location of the defect, its size and whether it is accompanied by other cardiac anomalies. With uncomplicated defects in the region of the membranous portion of the septum there may be no symptoms whatever. In such



cases the individual may reach middle life without suffering any ill-effects. The same is true of small defects in the lower portion of the muscular septum as in Case II. Where the defects are large, and particularly if other anomalies are present, cyanosis and dyspnea are the rule. Attacks of syncope following any exertion as described in Case I are not uncommon. These patients are prone to develop infections, particularly endocarditis and pulmonary tuberculosis.

The physical signs resulting from defects in the septum are described in detail by Abbott.<sup>3</sup> They are most intense over the central portion of the precordium, over the third and fourth ribs, just to the left of the sternum, because the septum is situated here. In brief there is usually hypertrophy of the right ventricle, and in the case of large defects precordial bulging and visible pulsation. A thrill can be felt directly over the septum, sometimes over the entire precordium. Murmurs, systolic as a rule, can also be heard best in this region and are not transmitted to the vessels of the neck. *The intensity of the murmur is not always commensurate with the size of the defect.*

On account of the interchange of blood between the two ventricles there is usually cyanosis. Hippocratic finger-tips and polycythemia are common accompaniments of the condition.

The two cases reported here are typical examples of congenital interventricular septum defects. Case I is an instance of multiple defect, being accompanied by pulmonary stenosis. This is a common combination and is attributed, according to the more recent theory of Keith, to an incomplete development of the infundibulum cordis. The defect in Case II is believed, in the absence of all signs of inflammatory reaction, to be congenital and due to incomplete development. By reason of its location it must be classed among the rare anomalies of the septum. The causes of developmental defects in this location are not understood.

---

## THE TREATMENT OF HYPERTOXIC CASES OF TYPHOID FEVER BY TRANSFUSION WITH RECENTLY ARTIFICIALLY IMMUNIZED BLOOD.\*

By LESTER NEUMAN, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY, MEDICAL SCHOOL, GEORGETOWN UNIVERSITY,  
WASHINGTON, D. C.

It is with a certain degree of temerity that I approach another discussion of so hackneyed a subject as typhoid fever. Since the

<sup>3</sup> Loc. cit.

\* Read before the District of Columbia Medical Society, November 30, 1921.

introduction of the name "Fièvre Typhoïde," by Louis,<sup>1</sup> in 1839, medical literature has been flooded with publications on this subject. A review of this literature is at once inspiring and instructive. No better example of scientific medical progress can be found in all history. Rational therapy depends upon an accurate differential diagnosis, and, in this instance, there is a striking example of the evolution of modern diagnostic methods; that is, the correlation of bedside observation and clinical experience and the more accurate laboratory methods.

It is not within the scope of this paper to review in detail the history of typhoid fever, with the exception of the progressive steps in the methods of treatment, especially specific therapy. However, one cannot pass without recalling a few of the salient facts in history to which are attached the names of the pioneers in this field.

Although this discussion is particularly in the interest of the treatment of typhoid fever along specific lines, and not those of a symptomatic nature, a few outstanding facts in the development of our ideas of the treatment of this disease cannot be ignored. No consideration of treatment would be complete without mentioning methods of prevention. This can be briefly discussed under three heads: (1) It might be possible to immunize all individuals; however, this immunity is not permanent and is only relative and might be overcome by a massive infection. (2) The destruction of all the organisms in the excreta, but this method offers the difficulty of discovering all carriers and the mild undiagnosed cases. (3) The protection of all foods and water by proper hygienic measures. Since none of these methods is flawless they are all of equal importance.

The rather unimportant role of drug therapy hardly merits discussion here. The introduction of a high caloric diet marks one of the great steps in advance in the treatment of typhoid fever. It has been shown by Coleman and DuBois<sup>2</sup> that a diet rich in carbohydrates maintains a nitrogen equilibrium best and prevents the great emaciation so often seen, and perhaps the cause of death in many cases. This conception of the dietary management of typhoid patients may be regarded as of equal importance with any other step forward in the conquest of this disease.

The judicious use of hydrotherapy is an important one, water being used both internally and externally. Of historic interest only is the Brand method of putting the patient in a tub bath at 65° F. Although heralded by Brand<sup>3</sup> as the ideal method of rapidly reducing the hyperpyrexia, it was found to be fraught with many dangers and has been generally discarded.

The use of typhoid vaccine as a therapeutic agent has been the source of many clinical experiments and reports. Fraenkel<sup>4</sup> was the first to use the vaccine by the subcutaneous method, followed

by Collison,<sup>5</sup> Krumbhaar and Richardson,<sup>6</sup> Zupink, Müller and Leiner,<sup>7</sup> and many others. They all report a reduction in the mortality and the length of the disease. Working independently, Ichikawa<sup>8</sup> and Kraus and Mazza<sup>9</sup> introduced the intravenous method with very striking results. Many cases showed a fall of temperature by crisis, and the duration and severity of the disease were materially reduced in many others. It was soon discovered, however, that the same results could often be obtained with any foreign protein, as other bacteria, proteose, albumose, etc. It has also been observed that this method is not unattended with danger.

Labbe and Moussand,<sup>10</sup> following the original work of Letulle and Mage,<sup>11</sup> used colloidal gold solution by the intravenous route in the treatment of moderately severe and grave cases. They report a reduction in the general symptoms of infection and intoxication, shortening of the disease and a reduced mortality.

The use of a specific immune serum would seem the logical treatment of typhoid fever from the theoretic standpoint, and this has been the goal of many investigators. Numerous immune sera obtained from animals, especially horses and goats, have been used. Most of them have been reported with great enthusiasm by the originator, but only with fairly encouraging results by the subsequent observers. Chantemesse<sup>12</sup> prepared a serum by injecting horses with a soluble typhoid toxin. His therapeutic dose is a very small quantity injected subcutaneously, and only one dose is used. His results in 1000 cases were very encouraging, the mortality being reduced to 4.3 per cent, a very low average for Paris at that time. Besredka<sup>13</sup> produced a serum by injecting horses with the endotoxins obtained from dried cultures of typhoid bacilli. The observations of Besredka and the other workers along this line have not been of any practical value. Ludke<sup>14</sup> prepared an antiendotoxic serum from goats, and reports encouraging results. Garbat and Meyer<sup>15</sup> report favorable experimental results with serum obtained by injecting animals with sensitized typhoid bacilli, and other animals with untreated organisms, pooling the sera of the two. Rodet<sup>16</sup> and his co-workers report the most favorable results in the treatment of typhoid fever with specific serum. He immunizes horses with living bouillon cultures and endotoxins. The immune serum is given in repeated subcutaneous doses, the quantity varying from 10 to 20 cc. He reports a marked shortening of the disease and a rapid reduction of the height of the temperature. His results have been confirmed by Odilhan,<sup>17</sup> and Remond and Minvielle<sup>18</sup> and others. Stokes and Fulton<sup>19</sup> report a serum obtained by injecting hogs with increasing doses of bouillon cultures, producing a serum with an agglutination titer of  $\frac{1}{1000000}$ . Its use in 23 cases showed favorable results.

Von Jaksch<sup>20</sup> (1895) was apparently the first to make use of the

immune serum of convalescents and the results obtained were very favorable. His work was confirmed a few years later by Walger<sup>21</sup> (1898). This fertile field of investigation, the use of immune human serum, remained untouched for almost ten years. Petrovitch<sup>22</sup> (1915) employed the serum of convalescent or immunized individuals in the treatment of 500 cases with a mortality of 4.3 per cent. In 1000 control cases treated without serum the mortality was 12.8 per cent. He usually used about 10 cc intravenously. This was done in the Serbian army.

Koenigsfeld<sup>23</sup> reports some very interesting experiments in the treatment of typhoid fever with the patient's own serum. He gives daily intravenous injections of serum in doses of 2.5 to 4 cc. In 26 cases treated there was a marked improvement characterized by a reduction of temperature, shortening of the disease, improvement in the sensorium, and especially good results in the comatose cases. These findings were confirmed by Meyer.<sup>24</sup>

The use of immune blood or blood serum from convalescents in the treatment of infectious diseases is by no means a new procedure. It has been attempted in a great variety of conditions. Scarlet fever has been treated by injections of blood serum and whole blood from convalescents, both subcutaneously and intravenously, with especially good results in the very toxic cases, as reported by Weaver.<sup>25</sup> The recent epidemics of influenza found many adherents of serotherapy, convalescent serum and whole blood being used intravenously. Favorable reports were made by Stoll,<sup>26</sup> and O'Malley and Hartman,<sup>27</sup> but the general consensus of opinion was not so encouraging. When it is remembered that the pneumonia complicating the influenza was the result of a secondary invader and that this secondary infection varied with the individual and the locality, the serum or blood in this instance cannot be properly classed as specific. Very recently convalescent serum has been used as a prophylactic and therapeutic agent in measles, and the results reported from Germany are exceedingly encouraging. Many other examples of attempted specific therapy using convalescent serum could be enumerated. However in none of them has it been possible to demonstrate any appreciable amounts of protective antibodies.

Typhoid fever presents an entirely different problem. By means of the well-known Widal reaction it is possible to demonstrate the agglutination titer of the serum. While there are probably many different protective antibodies in the circulating blood, this is our only index. The Widal reaction is present for a relatively short time in low dilutions after convalescence, and for a longer period and in much higher dilutions after artificial immunization. Nevertheless the immunized individual, both convalescent and artificial, shows great resistance to infection long after the disappearance of the agglutinins, especially the convalescents. This clearly

indicates that there is a cellular immunity in addition to the circulating or humoral immunity. *The great excess of the circulating immune bodies in the artificially immunized is of great practical importance in the serotherapy of typhoid fever.*

The previous attempts at specific therapy in typhoid fever, using immune human serum, as mentioned above and reported by von Jaksch,<sup>28</sup> Walger,<sup>29</sup> Petrovitch,<sup>30</sup> and Garbat,<sup>31</sup> failed to appreciate the quantitative differences in the antibody content of convalescent and artificial immune serum. In most of the cases only convalescent serum was used. When one remembers that many convalescent sera show a very low agglutination titer, and occasionally none at all, it is not surprising that these earlier results were not regarded with any great enthusiasm. In the few instances in which artificial immune serum was used very little regard was paid to the length of time after immunization, so that the serum was not obtained at the peak of the antibody content. Furthermore, very small doses of serum were used. This was, of course, a necessity in dealing with convalescents. However, the passive immunity conferred must have been comparatively small.

The present method is attempted in the light of modern theories and experiences in immunity as especially related to typhoid fever. To summarize these very briefly: The immunity produced through infection by the *Bacillus typhosus* (or the para A and B) shows a very high cellular immunity but a relatively small content of circulating antibodies, the latter rapidly disappearing during convalescence. The immunity produced by prophylactic inoculations shows a very high content of circulating antibodies, disappearing rather slowly, and a relatively low cellular immunity. The index of circulating antibodies is the agglutination titer, no other satisfactory one being available, although it must be realized that the agglutinins represent only one of a number of protective substances.

If the foregoing hypotheses be true, and experience and experiment point in that direction, then the use of blood from recently artificially immunized individuals would seem to be the proper procedure, especially in the very toxic cases. On theoretic grounds the use of whole blood in large quantities offers many advantages. The larger quantities (500 to 700 cc) furnish a great amount of protective substances. The inclusion of the cellular elements of the blood furnishes additional coagulating properties, much needed leukocytes and the red blood cells combat the anemia and emaciation and stimulate the bone-marrow, thus aiding red and white blood cell formation. The use of the large quantity of blood also obeys the well-established rule of serotherapy that an excess of serum should always be employed.

The following two cases are then presented in the way of a preliminary report in support of these theories:

CASE I.—E. W. T., male, aged thirty-six years; occupation, clerk.

*History.* The family history was negative. He had measles and mumps as a child. In 1906 he had a continued fever lasting three weeks, which was said to be typhoid fever, but without laboratory confirmation. He is a great user of tobacco, both smoking and chewing. For the past eight years he had been a constant user of alcohol, consuming about one pint of whisky daily and occasionally a larger amount. He is married and has three healthy children.

The patient was first seen on June 4, 1921, by Dr. E. W. Birch. For two weeks he had been complaining of a moderate malaise and headache, and there had been a nose-bleed one week previously. A specimen of blood taken on June 5 and reported on June 6 showed a positive Widal with the *Bacillus typhosus*. The patient resided at Fort Meyer Heights, Va., a suburb of Washington, but there had been no other cases of typhoid fever in the immediate vicinity. The well-water on this place showed no fecal contamination and no other members of the family were affected. It was later learned that the patient was very fond of raw oysters and had eaten them frequently during the previous month. On June 7 he was removed to the Sibley Hospital.

June 7 to June 19. The temperature on admission was 104.4°. During this period of twelve days there was practically a continuous temperature, with a minimum of 102.6° and a maximum of 104.6° by the axilla. He was constantly irrational and semicomatose.

June 20 to June 25. During this period of six days the diurnal temperature variations were greater, with a minimum of 99° and a maximum of 103.6°. The delirium and semicoma continued. On June 25, the twenty-second day of the illness, there was a profuse intestinal hemorrhage, accompanied by rapid pulse (160 per minute), pallor, rapid sighing respirations, sweating and collapse. There were no symptoms of perforation. Dr. Thomas A. Claytor saw the patient in consultation and advised blood transfusion, although he gave a very poor prognosis. The writer then saw the patient for the first time for the purpose of transfusion. 600 cc of blood was given by the citrate method, with a very rapid and marked improvement. The blood-pressure before transfusion was 100 mm. and afterward was 108 mm. systolic. The temperature fell to 98° after the hemorrhage, but by the next day was 103.6°.

June 26 to July 4. During this period of eight days following the transfusion the condition of the patient was fairly good. The temperature varied between 100° and 104.2°, with a continuation of the delirium.

July 3 a small quantity of food was given by mouth, the first since the hemorrhage. This was followed by a profuse intestinal

hemorrhage. A transfusion of 700 cc was again given (thirtieth day of illness). The symptoms of collapse present after the first hemorrhage were again in evidence, and were as rapidly and effectually ameliorated by the transfusion.

July 5 to July 7. The temperature continued high after the second transfusion, and for this period of three days varied between 100.8° and 104°. However the patient's general condition was not very satisfactory. The delirium was more marked, alternating with periods of complete coma. The emaciation was extreme, and there was a very rapid and shallow pulse. In view of the poor condition of the patient and the catastrophe following the ingestion of food after the first transfusion the writer suggested that another transfusion be given in place of food. It was realized that 600 or 700 cc of blood represented more food than this patient could take in by mouth for quite a few days, that the normal blood might contain some natural protective substances, and, fortunately, there were plenty of donors available. Therefore on July 7 (thirty-third day of disease) a transfusion of 700 cc was given. There was no reaction and the only result of this treatment was some improvement in the patient's general condition. The temperature curve showed no essential changes.

July 8 to July 15. The temperature for this period of seven days following the third transfusion of normal blood varied between 99.6° and 104°. There was no abatement of the very toxic symptoms as enumerated above. Both nurses on the case had offered to be donors, and since both had been artificially immunized when beginning duty on this case it was deemed advisable to try the effect of transfusion with recently immunized blood. Only one of the bloods was found to be in the proper iso-hem-agglutinin group. The Wassermann was negative and the serum was found to have a very high agglutination titer (typhoid,  $\frac{1}{128000}$ ; paratyphoid A,  $\frac{1}{16000}$ ; paratyphoid B,  $\frac{1}{32000}$ ). She had received three doses of the Army Medical School triple vaccine, at one week intervals, and had received the last dose on June 23, 1921, so that this represented the twenty-first day after the last injection.

July 25. A fourth transfusion of 500 cc was given, but this time with recently artificially immunized blood. This was the fortieth day of the disease and the temperature was 103° just before the transfusion. There was no reaction.

July 16 to July 30. On the day following the fourth transfusion the maximum temperature was 100° and by the following day it was 99.2°. During this period of fifteen days the temperature was practically normal, varying between 97.6° and 99.6°. The symptoms of extreme toxemia improved very rapidly. Whereas the temperature was practically normal within thirty-six hours of this transfusion the delirium had practically disappeared in forty-eight hours. The pulse and respirations also showed a proportionate

improvement. From this time up to July 30 the condition was one of steady improvement. Food was again allowed in the middle of this period.

July 31 to August 13. On July 31, the fifty-eighth day of the disease, there was a recrudescence of the fever. For the next fourteen days it varied between  $99.8^{\circ}$  and  $101.4^{\circ}$ , but there was no return of the delirium, coma, rapid pulse or other toxic symptoms, and the patient continued to take his food without mishap.

August 14 to August 28. This period of fourteen days marked one of steady improvement. The temperature remained normal with the exception of an occasional rise to  $99^{\circ}$ . He was discharged from the hospital on the eighty-sixth day of the disease.

After a rest of about one month at home he has returned to his work. Upon questioning it is interesting to learn that he remembers nothing of his stay in the hospital until the middle of the first period of normal temperature, about four days after the fourth transfusion. He does not recall anything about the transfusions.

*Laboratory Data.* The Widal reaction done on June 6 and June 18 was strongly positive with the *Bacillus typhosus*. The leukocyte counts were as follows: June 6, 2900; June 17, 2200; June 23, 1900; June 28, 3600; July 1, 2700; July 6, 4700. It is interesting to note the rise of leukocytes following transfusion. The erythrocyte counts and hemoglobin estimations made before and after the first two transfusions are not included in this report, as there was some question as to their accuracy. Urine examinations were made at various periods of the case, and there were no pathologic changes with the exception of a faint trace of albumin and a few casts. Both of these disappeared during convalescence.

A summary of this case presents a few outstanding features: the value of transfusion in typhoid hemorrhage is clearly demonstrated in spite of the misgivings expressed in practically every standard text-book. The timeworn axiom that blood-pressure is raised and bleeding increased is a fallacious one, as the systolic pressure is usually only raised from 8 to 10 mm., certainly not enough to increase hemorrhage. The use of blood as a supportive measure and as food in such a case, where there is great inanition and where food is contraindicated, would seem to be of value. But the most striking feature is a comparison of the results of the four transfusions. Three transfusions of normal blood alleviated the symptoms of hemorrhage in two instances and acted in a supportive manner in a third, but the temperature and toxemia were in no way affected. The fourth transfusion of recently artificially immunized blood produced a prompt fall in temperature and a rapid disappearance of the symptoms of toxemia.

CASE II.—A. L. G., female, single, aged twenty-six years, occupation, school teacher.



*History.* With the exception of mumps, measles, and chicken-pox in childhood the patient has never been ill. She has always been very robust and athletic. The family history is uninteresting. The last two weeks of August, 1921, were spent on a farm. On September 6, 1921, she complained of a dull headache and of general muscular pains. Home remedies were tried for several days, but as the symptoms did not disappear and there was an increasing stupor the writer was consulted.

September 9, 1921. The patient was a young woman, quite robust, and appearing very stuporous. A general physical examination was negative with the exception of a markedly coated tongue, tympanites and sluggish reflexes. The temperature was  $103.8^{\circ}$ , respirations 18 per minute, and the pulse 62 per minute, and slightly dierotic.

September 10 to September 18. During this period of nine days the temperature varied between  $101.2^{\circ}$  and  $104.6^{\circ}$ . There was a gradually increasing stupor, but the patient could be aroused by persistent stimulation. The regimen consisted of sponge baths for hyperpyrexia and a high caloric diet. The blood culture, taken on September 14, was positive for the *Bacillus typhosus*.

September 19 to September 30. This period was marked by an almost continuous fever, varying between  $103^{\circ}$  and  $104.8^{\circ}$ . The stupor had now become complete and there was a delirium, sometimes of the low muttering type and sometimes very agitated. There had been no evidence of hemorrhage or perforation, but the emaciation was extreme. When the diagnosis of typhoid fever had been made all the members of the family had been given typhoid vaccine as a prophylactic. There were two brothers, one of whom was in the same iso-hem-agglutinin group as the patient. With the possibility of using his blood the intervals between his doses of vaccine were shortened to five instead of seven days. He had therefore received his last injection on September 20, 1921. The vaccine used was the triple vaccine of the U. S. Army Medical School. The agglutination titer of his blood serum was  $\frac{1}{100}$  for the *Bacillus typhosus*,  $\frac{1}{100}$  for *Bacillus paratyphosus* A and  $\frac{1}{100}$  for *Bacillus paratyphosus* B. In view of the increasing toxemia and emaciation 650 cc of the recently artificially immunized blood of the brother was given. The temperature just before the transfusion was  $104^{\circ}$  (September 30, the twenty-fifth day of the disease).

October 1. The patient's general condition is greatly improved. She is much more quiet, takes nourishment better and the maximum temperature was  $102.2^{\circ}$ .

October 2. The temperature on the second day following the transfusion was practically normal: maximum  $99.2^{\circ}$ , minimum  $97.8^{\circ}$ . There is a continuation of the general improvement and much less evidence of toxemia.

October 3. The temperature remained normal and the delirium had entirely disappeared. The patient would now answer questions by nodding the head. Aside from a tremendous asthenia all evidence of the profound toxemia had disappeared on the third day following the transfusion.

October 4 to October 29. This period was one of a slow convalescence. For the first week the temperature would occasionally reach 99.6°. The patient gradually gained weight and strength. When questioned she said that she did not recall the transfusion in any way, and, in fact, she had no recollection of anything from the fourth day after she went to bed until four days after the transfusion.

*Laboratory Data.* Blood culture on September 14 was positive for *Bacillus typhosus*. September 10: Erythrocytes 4,645,000, leukocytes 5600, hemoglobin 82 per cent (Dare). The following additional leukocyte counts were made: September 15, 4400; September 19, 2950; September 28, 2100; October 3, 4900. (Note rise of leukocytes after transfusion.) Widal reaction on September 20 and 29 were positive with the *Bacillus typhosus*. The *Bacillus typhosus* was found in the urine and the feces. Urine examinations were made at various times. There were no pathologic changes with the exception of a trace of albumin and a few leukocytes and casts, all of which disappeared during convalescence.

One aspect of the typhoid question that naturally presents itself is the question of the necessity for further developments in treatment when our present-day methods of prevention are so well advanced. A study of the available statistics shows that we have beguiled ourselves with a false sense of security. The most recent complete report is contained in the *Twentieth Annual Report of the Bureau of the Census, Mortality Statistics*, for 1919: "The number of deaths from typhoid fever in 1919 is 7860, corresponding to a death-rate of 9.2 per 100,000 population, which is much lower than the rate for 1918 (12.6), and is the record low rate in the period of twenty years from 1900 to 1919 inclusive. It is based on transcripts of death certificates received from the registration area for deaths, which in 1919 had an estimated population of 85,400,437, or 81.2 per cent of the total estimated population of the United States and the territory of Hawaii." It is safe to assume that the total deaths from typhoid fever in this year is about 10,000. The only available data for 1920 is contained in the ninth annual survey of the large cities (100,000 or more).<sup>32</sup> A study of this report shows a very slight general decrease in the death-rate, but even cities with very low averages show an occasional outbreak. The situation in 1921 does not seem to be so favorable. I shall quote from the *Statistical Bulletin*, Metropolitan Life Insurance Company, October, 1921:

"What is the significance of the remarkable increase in the number of deaths from typhoid fever during the months of August and September of this year? The first six months of the year closed without any indication of a check in the rate of decline for this cause of death. The figures for Metropolitan Industrial policyholders for the period January to June showed that there had been a decline of 14 per cent in the typhoid fever death-rate among white persons and 15 per cent among colored persons as compared with the rate of the first six months of last year. But the number of deaths during the third quarter of 1921 has been so large that at the present writing the typhoid fever death-rate for this year to date equals that of last year and is still rising. Unless there is a change in the present situation the year 1921 will close with a higher death-rate for typhoid fever than did 1920.

"From various parts of the country come reports showing that we are right now experiencing numerous local epidemics of typhoid fever. There has been unusual prevalence of the disease in the states of New Jersey, Illinois, Pennsylvania, Ohio, New York, North Carolina, Maryland, Georgia, Indiana, Alabama, Kentucky, and Kansas.

"The facts for the last few months indicate that there has been a slackening in the control of this disease. This does not necessarily mean that we shall go back to the periods of high typhoid fever death-rates. With our present-day knowledge of the causes and means of control of typhoid fever we shall probably never again suffer from the high rates of ten years ago. Nevertheless, the check in the decline of the death-rate is a source of great disappointment and suggests further inquiry as to what is at the bottom of the change. Is it necessary in certain states and cities for the health departments to tighten up their control of the sources of distribution of their milk supplies? Has there been any let-down in the sanitation and supervision of water supplies? Are the precautions against carriers as rigidly carried out as they have been in the past? Is the good effect of war-time inoculation wearing off? Is the distribution of antityphoid literature as general or as effective as heretofore? Are markets and other places where food is handled inspected with as much care as formerly?

"These are some of the questions which health officers and sanitarians must ask in view of the recent increase in the typhoid fever death-rate. We have with good reason begun to look upon typhoid fever as a vanishing disease. It is obvious that there is still much work to be done unless we are willing to continue in the unsatisfactory condition of either a stationary or a rising death-rate from typhoid fever."

The method and length of time required to produce a satisfactory artificial immunity is a matter of prime importance and possibly one of the real objections to this method treatment. Time

does not permit a lengthy discussion of this subject here, but a few fundamental facts will be stated. Since the pioneer work of Wright,<sup>32</sup> Pfeiffer and Kolle,<sup>33</sup> and Russell<sup>34</sup> there has been a constant discussion as to the relative value of vaccination with killed cultures, live cultures and sensitized organisms, and also as to the number and size of the dose and the time interval. It has been used on a large scale in the recent war on large bodies of men under control, and the results have been most excellent in all of them, although the methods differed. The British and American armies used killed cultures in a triple vaccine, containing a single strain each of the *Bacillus typhosus*, paratyphosus A and paratyphosus B, thus constituting a monovalent vaccine. The British used two doses and the Americans three doses at weekly intervals. The French army used a similar vaccine, except that at the direction of Vincent it was made polyvalent, that is, it contained ten strains of the *Bacillus typhosus* and single strains of the other two organisms. Vincent recommended the use of four doses at weekly intervals, but due to the exigencies of war reduced it to two. The efficacy of the killed culture vaccine as produced at the U. S. Army Medical School and used with remarkable success in millions of individuals during the past few years cannot be questioned. Similar ones are prepared by various boards of health and also commercially. They usually contain 1000 million *Bacillus typhosus*, 750 million *Bacillus paratyphosus* A and 750 million *paratyphosus* B per cc. The dosage is usually 0.5 cc, followed at weekly intervals by 1 cc, three doses in all. By the end of the first week after the last injection the agglutination titer frequently has reached  $\frac{1}{10000}$  or  $\frac{1}{20000}$ , and in ten days it is frequently  $\frac{1}{50000}$  or better. However, the time required to obtain a satisfactory antibody content in the blood is, at the minimum, about three weeks. To be of service in the suggested method of treatment this period of immunization must be shortened.

Gay<sup>35</sup> has been able to obtain very satisfactory immunity by giving the doses on alternate days instead of alternate weeks, and believes it could be accomplished by a single dose containing the same number of organisms as the three. It is possible, however, that such a dose might be overwhelming. The crux of the situation may be well defined by quoting Vincent and Muratet.<sup>35</sup>

"What is the quantity of vaccine needed to confer immunity and what is the duration of this immunity? As a matter of fact the immunity and its duration are in direct relation not to the number of the injections, nor even, properly speaking, to the quantity of vaccine injected, but to the number of typhoid bacilli injected."

Vincent further believes that the minimum protecting dose of antigen is between 1300 and 2000 million bacilli. Therefore it is proposed to use, for the purpose of producing a rapid artificial

immunity, the vaccine of the U. S. Army Medical School, or a similar one, in three doses of 0.5 cc, 1 cc and 1 cc on alternate days.

**Comment.** Two cases of typhoid fever of the hypertoxic type are presented. Both were treated with recently artificially immunized blood, and the result in each case has been unusually gratifying. It is not presumed to draw any definite conclusions from two cases. However, a few possibilities suggest themselves.

1. This is not intended as a general treatment for typhoid fever. The mild and moderately severe cases will respond to careful nursing and a high calorie diet.

2. The rationale of this treatment is founded on experimental and clinical facts as they pertain to typhoid immunization.

3. Parenthetically, transfusion for hemorrhage in typhoid fever is justifiable and is the treatment of choice.

4. In this age the opportunity will come to no one man to apply this form of treatment to a large series of cases. It is to be hoped, therefore, that it will be used in the isolated cases and the cases recorded. In this way only will its ultimate usefulness be established.

5. Perhaps it is too much to hope that this may mark the beginning of another epoch in the conquest of this disease and that the annual toll of ten thousand lives in the United States may be reduced to that many hundred.

#### REFERENCES.

1. Recherches anatomiques pathologiques et thérapeutiques sur la maladie connue sous les noms de fièvre typhoïde, J. B. Baillière, 1841.
2. Calorimetric Observations on the Metabolism of Typhoid Patients with and without Food, Arch. Int. Med., 1915, 15, 887.
3. Die Hydrotherapie des Typhus, Stettin, 1861.
4. Ueber spezifische Behandlung des Abdominal typhus, Deutsch. med. Wchnschr., 1893, 19, 985.
5. Therapeutic Use of Vaccine in Typhoid Fever, AM. JOUR. MED. SC., 1912, 144, 350.
6. The Value of Typhoid Vaccine in the Treatment of Typhoid Fever, AM. JOUR. MED. SC., 1915, 149, 406.
7. Erfahrungen über Praxis und Theorie der Vakzintherapie, Wien. klin. Wchnschr., 1916, 29, 33.
8. Abortivbehandlung von typhösen Krankheiten, Mitt. d. med. Gesellsch. z. Tokio, 1914, 33, 21.
9. Zur Frage der Vakzintherapie des Typhus abdominalis, Deutsch. med. Wchnschr., 1914, 49, 1556.
10. Traitement de la fièvre typhoïde par l'or colloïdal, Presse méd., Paris, 1916, 14, 105.
11. Traitement de la fièvre typhoïde par l'or colloïdal en injections intraveineuses, Bull. Acad. Méd., Paris, 1914, 72, 421.
12. Toxine typhoïde soluble et serum antitoxique de la fièvre typhoïde, Prog. méd., 1898, 7, 245.
13. De l'immunisation active contre la peste, le cholera et l'infection typhique, Ann. Inst. Pasteur, Paris., 1902, 16, 918.
14. Ueber die Gewinnung und Wirkung von Typhusheilserum, Deutsch. Arch. f. klin. Med., 1910, 98, 395.
15. Ueber Typhus-Heilserum, Ztschr. f. exper. Path., 1910, 8, 1.
16. Serothérapie antityphoïdique, Bull. de l'Acad. de méd., Paris, 1916, 76, 114.

17. La Sérothérapie de la Fièvre Typhoïde par le sérum du Professor Rodet, *Presse méd.*, Paris, 1918, 15, 473.
18. Traitement de la fièvre typhoïde par le sérum de Rodet, *Bull. l'Acad. de méd.*, Paris, 1915, 73, 321.
19. A Bacteriologic and Clinical Study of a Curative Serum for Typhoid Fever, *Jour. Am. Med. Assn.*, Chicago, 1905, 44, 1504.
20. Ueber die Behandlung des Typhus abdominalis mit Blutserum von Typhus-rekonvalenszenten, *Verhand. d. Kong. f. inn. Med.*, Wiesbaden, 1895.
21. Beitrag zur Behandlung des Typhus abdominalis mit Menschlichen Rekonvalenszentenblutserum, *Centralbl. f. inner. Med.*, 1898, p. 941.
22. Traitement de la fièvre typhoïde par hémosérothérapie dans l'armée serbe, *Presse méd.*, Paris, July 29, 1915.
23. Ein neues Prinzip der Serumtherapie bei Infektionskrankheiten mit besonderer Berücksichtigung des Typhus abdominalis, *Deutsch. med. Wchnschr.*, 1915, 41, 755.
24. Zur Behandlung des Typhus mit Eigenserum, *Therap. d. Gegenw.*, Berlin, 1915, 57, 176.
25. Further Observations on the Treatment of Scarlet Fever with Immune Human Serum, *Jour. Am. Med. Assn.*, Chicago, 1919, 73, 478.
26. The Value of Convalescent Blood and Serum in the Treatment of Influenza Pneumonia, *Jour. Am. Med. Assn.*, Chicago, 1919, 78, 478.
27. The Treatment of Influenza Pneumonia with Plasma of Convalescent Patients, *Jour. Am. Med. Assn.*, Chicago, 1919, 52, 34.
28. *Loc. cit.*
29. *Loc. cit.*
30. *Loc. cit.*
31. Convalescent Typhoid Serum in Treatment of Typhoid Fever, *Jour. Immunol.*, Baltimore, 1916, 1, 387.
32. Typhoid in the Large Cities of the United States in 1920, Ninth Annual Report, *Jour. Am. Med. Assn.*, Chicago, 1921, 76, 860.
33. Remarks on Vaccination against Typhoid Fever, *British Med. Jour.*, January 30, 1897, p. 256.
34. Experimentelle Untersuchungen zur Frage des Schutzimpfung des Menschen gegen Typhus abdominalis, *Deutsch. med. Wchnschr.*, 1896, 22, 735.
35. Progress in Antityphoid Vaccination during 1912, *Jour. Am. Med. Assn.*, Chicago, 1913, 61, 665.
36. Typhoid Fever, p. 165.
37. Typhoid Fevers and Paratyphoid Fevers, 1917; translated by J. D. Rolleston, p. 266.

## CONGENITAL ABSENCE OF THE SPLEEN.

BY STAFFORD MCLEAN, M.D.,

AND

HOWARD R. CRAIG, M.D.,

NEW YORK.

(From the Babies' Hospital.)

OF all the anomalies relating to the viscera, congenital absence of the spleen is one of the rarest. It occurs as a single abnormality, but more frequently is associated with one or more congenital malformations. In all the reported cases it was an accidental discovery at autopsy. Some of the cases occurred in infants while others were in adults who at no time had discoverable symptoms referable to the absence of an important viscus.

CASE REPORT. Andre P., aged three months, of French parentage, was first seen by one of us on November 15, 1921, and on that

day was referred to the Babies' Hospital for admission, where he was under observation for nineteen days.

The patient was the third of three children. The others were apparently normal in every respect. The child was born at full term after normal delivery and the birth weight was recorded as nine pounds. The infant had not been nursed at any time. He had been fed on mixtures of whole milk, water and milk-sugar with small amounts of wheat flour. The stools had been normal; there had been no vomiting, but the child did not thrive. Prior to the onset of the symptoms, which were the cause of his admission to the hospital, the weight had been recorded as nine pounds.

The symptoms noted by the parents had been "cold in the head" associated with fever as high as 103° F. for one week, and rapid respiration, which was first noted the day prior to admission to the hospital.

*Physical Examination.* On examination the infant was found to be moderately well nourished and well developed. He looked acutely ill but was not greatly prostrated. Some dyspnea was evident and the skin of the entire body was slightly cyanotic. The weight was 3700 grams.

The measurements were: Head, 14 inches circumference; chest, 13 inches circumference; abdomen, 11 inches circumference; length, 22½ inches circumference. Distance from top of cranium to umbilicus, 12 inches; distance from the umbilicus to the sole of foot, 10½ inches; the anterior fontanelle measured 2 x 2 inches.

The posterior fontanelle was closed. The pupils reacted to light. The ears were normal and the right ear was slightly larger than the left. The lips were of a darker hue than the rest of the body. The throat was normal. The superficial lymph glands were not enlarged. The chest was of normal contour; the respiratory movements were somewhat limited and there were well-marked supra- and infraclavicular retraction. The maximum cardiac impulse was just below the xiphoid cartilage. The right border of the heart, as determined by percussion, was one inch to the right of the midsternal line and the left border two inches to the left of the same line. There was a distinct cardiac murmur heard over the entire precordium and also over the right chest posteriorly. It was systolic in time and transmitted to the vessels of the neck.

The lungs were apparently normal except for the presence of a few scattered moist rales heard at the bases behind. The abdomen was soft and slightly distended. There was a large mass, apparently liver, which occupied the upper quarter of the abdominal cavity. To the right of the midline the lower edge of this mass was horizontal and could be felt about one inch below the costal margin. To the left of the midline the lower edge ran obliquely downward and to the left, disappearing in the flank, where it was felt about two

inches below the free border of the ribs. The reflexes were normal. A left-sided hydrocele of the cord was present.

*Clinical Course.* During the infant's period of observation in the hospital fever was constantly present, fluctuating between  $100^{\circ}$  and  $102^{\circ}$ . For the first ten days he maintained his admission weight of 3700 grams and from then on steadily lost. His weight on the day of discharge was 3500 grams. The stools were normal for the first ten days of hospital observation. During the balance of the period they became more frequent, generally four or five in twenty-four hours. On the seventeenth day both ear-drums were incised and pus obtained.

A routine throat culture was done. This showed no Klebs-Loeffer bacilli. Both the von Pirquet test and the intracutaneous tuberculin test were negative. The urine was straw-colored, clear, acid, contained considerable albumin, a few white blood cells and many hyaline and granular casts. There was no sugar or acetone present. In a second urine examination, a few days later, albumin was present in the same proportion as previously reported, but no casts. One blood examination was done four days after admission. The hemoglobin was 100 per cent. White blood cells numbered 33,300, and were differentiated as follows: Polymorphonuclears, 66 per cent; eosinophiles, 3 per cent; small lymphocytes, 20 per cent; large lymphocytes, 5 per cent; large mononuclears and transitionals, 6 per cent. The platelets were increased in number.

Two roentgenographic examinations were made of the trunk. Both of these showed a cardiac shadow which extended considerably beyond the normal, both to the right and to the left. The liver shadow approximated the findings outlined by palpation as noted above, which proved at autopsy to be a transposition of the right and left lobes.

The infant was removed from the hospital nineteen days after admission; two days later severe respiratory symptoms developed, and he died at home the following day, December 6, 1921.

The autopsy was performed at the Babies' Hospital by the hospital pathologist, Dr. Martha Wollstein. The findings were as follows:

- Anatomic Diagnosis:*
1. Congenital absence of the spleen.
  2. Congenital malformation of the heart (open auricular and ventricular septa—transposition of veins).
  3. Congenital malformation of the lungs (supernumerary lobes).
  4. Atelectasis and bronchopneumonia.
  5. Congenital malformation of the liver (transposition of right and left lobes).

The body was that of a well-developed and fairly well-nourished white male infant. No skin lesions were present.



*Lungs.* No pleurisy. Left lung had three lobes divided by two well-marked fissures. It was well aerated throughout. The right lung had four lobes, *i. e.*, in addition to the three normal lobes there was a triangular lobe separated from the lower lobe by a well-marked fissure and corresponding to the sublingual lobe in the dog. In addition the right lower lobe had a small fissure near its upper angle extending about 3 cm., so that there was an incomplete fifth lobe. The right lower lobe was blue in color, smaller than the left lower, partly atelectatic and partly, in its anterior portion, the seat of a bronchopneumonia.

*Bronchial Lymph Nodes.* Normal.

*Heart.* Normal in position, pointing to the left and larger than normal. At the base it measured 5 cm. in diameter. In length it measured 6 cm. The apex was very round, and there was a shoulder to the right ventricle, which made the base wider than normal. The auricular appendages were much rounded. Both auricles were distended with softly clotted blood, making the appendages seem longer than usual. The ventricles were of about the same size and thickness. The pulmonary artery and aorta were normal. The ductus arteriosus was closed. The foramen ovale was very widely open. The interventricular septum had a large opening, 1.5 cm. in diameter, in its upper third. The venæ cavæ emptied into the left auricle and the pulmonary veins into the right auricle. The valves were all normal.

*Liver.* The liver measured 14 cm. transversely. The larger lobe was on the left side and its anteroposterior diameter was 8 cm. The smaller right lobe measured 6.5 cm. anteroposteriorly. The suspensory ligament and the inferior fissure were to the right of the gall-bladder, which was in the left lobe. The other lobes of the liver were normal. On section the liver substance was congested, but otherwise normal.

*Spleen.* Completely absent. No supernumerary spleens found after prolonged search. The celiac axis had been removed, so that search for the splenic vessel could not be made.

*Kidneys.* Lobulated and on section congested, with markings blurred. Cortex was not thickened.

*Suprarenals and Pancreas.* Normal.

*Stomach and Intestines.* Normal throughout. The cecum was in its normal position on the right side. The appendix was normal. Cecum and mesocolon were very freely movable.

Smears from the heart's blood were taken at autopsy and stained with Wilson's stain. They showed no abnormal forms of cells. The polynuclear leukocytosis noted during life was evidently due to the bronchopneumonia present, and there was nothing in the blood morphology to indicate any abnormality of the lymphatic system.

**Discussion.** In the most recent publication regarding the spleen, Sir Berkeley Moynihan states the following: "The spleen is not always present in man, though its absence is excessively rare. Its occasional absence is noted in animals. In the vertebral kingdom its position is not constant. In the majority of animals it is outside but associated with the gastric segment; but there are instances of its development in connection with the lower end of the canal and others where it is scattered." In many of the text-books of pathology and pathologic anatomy, such as Aschoff, Ribbert, Ziegler and Delafield and Prudden, it is stated that cases of complete absence of the spleen have been known to occur. In the *American Text-book of Pathology* the following statement regarding this condition is made: "Complete absence of the spleen is rare. In these cases the organ is usually represented by several small scattered masses of splenic tissue (splenunculi) which, on account of their size and location, are in danger of being overlooked." Kaufman also noted that "Absence of the spleen occurs but seldom," and he adds the interesting comment that the disappearance might occur in fetal life from an embolus of the splenic artery. Adami and Nichols observe that complete absence of the spleen is the rarest of the congenital anomalies affecting the spleen and that it is frequently found associated with other grave defects of development. "About thirteen cases are on record, but only one, that of Birch-Hirschfeld, is beyond cavil. More often the place of the spleen is taken by scattered nodules of splenic tissue in various parts (splenunculi)."

They refer to Albrecht's case, in which there were nearly four hundred of these splenunculi scattered throughout the abdominal cavity. This condition was present in a twenty-six-year-old man who died of nephritis. The normal splenic organ was wanting in this individual, and these accessory spleens varied greatly in size, the smallest being only as large as the head of a pin. In the case of congenital absence of the spleen reported by Sternburg the patient was a woman, aged seventy-three years, who had had four normal pregnancies and had had "lung trouble" for a long period of years. She died shortly after admission to the hospital, and at autopsy it was discovered she had advanced pulmonary tuberculosis. There was no spleen found nor any accessory spleens. The retroperitoneal lymphatics were not enlarged. The branch of the celiac artery, which should have corresponded to the splenic artery, was broken up into a series of small twigs, which passed in part to the stomach and in part to the colon. Sternburg quotes an article by Toldt, which we have not been able to locate, in which 17 cases had been collected, and of these only 4 were unassociated with other abnormalities. In the other 13 there were abnormalities of different grades; 11 of the cases were in the newborn or in infants in the first weeks of

life and 6 were among adults. These adults varied in age from eighteen to forty-nine years of age and in only 3 of these was the absence of the spleen the only abnormality found. Birch-Hirschfeld's case was noted in an infant who died directly after birth. The infant was well nourished and well developed, but the liver was very large. The spleen and the splenic vein were absent but the portal vein was normal.

In 1871, when this report was presented by Birch-Hirschfeld, he stated that he could find no other cases in the literature except one,\* which was not accessible.

Glinski reported a case of a woman, aged forty-five years, who died of pulmonary tuberculosis. There were no other abnormalities noted at autopsy, no lymphatic hypertrophy, nor hypertrophy of other organs. Riches reported a case of a woman, aged forty-five years, who died in an institute for the insane following an operation for a round-cell sarcoma. He noted that this neoplasm occupied the site of the omentum; there were secondary deposits in the mesentery and lymphatic glands in the immediate vicinity of the growth. The autopsy findings failed to reveal any congenital abnormalities and careful search failed to reveal the presence of the spleen. Rose's case from Georgetown, British Guinea, occurred in a negro, aged fifty-six years, who died following an operation for strangulated hernia. At autopsy no spleen was found nor was there any splenic artery. He mentions the fact that there were no splenunculi present.

Hodenpyl's case, which he termed "apparent absence of the spleen," occurred in a negro, aged thirty-two years, who died after an illness of a week's duration. A compensating hyperplasia of the mesenteric and retroperitoneal lymph glands was present as well as a lymphatic hyperplasia of the suprarenals, the intestines and a cellular proliferation of Glisson's capsule.

The case reported by Martin in 1826 was in an infant, aged eight and a half months, who died following a series of convulsions. There was no spleen found at autopsy. The stomach was on the right side; above, it touched the liver and the diaphragm. The greater curvature touched the right kidney and the lesser touched the vertebral column, the head of the pancreas and the abdominal aorta. The first part of the duodenum was on the left side but the rest of the intestine was normal. The liver occupied both hypochondriac regions and was divided into two parts of equal size. The heart was large and the pulmonary artery and aorta were transposed. The auricles were large and communicated with each other. Each auricle furnished a superior and inferior vena cava. There was a single ventricular cavity, and, as Martin states, the heart resembled the heart of a fish.

\* Pohl, Lips, 1740, *De Defectu Lienis*.

Koch and Wachmuth's case occurred in a well-nourished and well-developed tinsmith, aged forty-nine years, who died of bronchopneumonia. At the autopsy the diagnosis was confirmed; all the organs were anatomically normal, but the spleen and splenic artery were absent. The case reported by Lebby in 1834 could hardly be classified as congenital absence of the spleen. This report concerned an adult negro (age not mentioned) who was executed and the body autopsied for the instruction of medical students. The negro was sixty-eight inches tall, badly nourished but well developed. He gave a past history of "bilious intermittent and remittent fevers." The author states that the spleen was absent, but relates further that "Contiguous to the pancreas was a sac the size of a large orange, oblong in form, of a dark ash color, shrivelled in appearance and imparting to the hand the sensation of squeezing a decayed orange; upon opening the sac it was found to contain pus of a creamy hue and consistency."

Ramsey's case also occurred in a negro slave, aged twenty-eight years, who had been ill for almost a year with intestinal symptoms accompanied by great loss of weight. At autopsy no spleen was found. As the author expressed it, "The spleen was wanting *in toto*, there was some suppurative matter about its situation, but nothing remained of it except a few ligamentous traces to mark the place of its existence." From this description one is obviously not justified in terming this case one of congenital absence of the spleen.

In an editorial notice in 1845, J. J. Sachs refers to a case reported before a Russian medical society the previous year by a Dr. Meinhard, of a woman, aged forty-seven years, who died in Peter-Paul's Hospital, in whom no trace of a spleen nor of splenic bloodvessels could be found at autopsy. There has evidently been some confusion in the literature regarding this case and the various references to it. Jelenski refers to this case and gives the age of the woman as fifty-seven years. Hodenpyl refers to the citation of Jelenski's and states that the latter mentions that Sachs performed an autopsy on an adult who had no trace of a spleen. As a matter of fact there was only one case, which was the one autopsied by Meinhard. Sachs merely referred to this case in an editorial note which was quoted by Jelenski thirty-five years later, and has since often mentioned as his own case.

Olaechea's case, with a carefully recorded autopsy, occurred in a young man who died of "tifomalaria." The age of the patient was not mentioned, but as he was a sergeant in a Peruvian regiment it may be assumed that he was a young man. At autopsy no trace of a spleen was found nor was there any evidence of suppurative splenitis. Fatty and connective tissue occupied the normal site of the spleen. There were no anomalies of the other organs, nor was there any scar of the abdominal walls through

which the spleen might have been previously removed. The liver was congested and there was a congestion of Peycr's patches, but no ulceration. The bronchial and mesenteric lymph nodes were greatly enlarged, some of the latter being  $2\frac{1}{2}$  cm. in diameter. The inguinal and axillary lymph nodes were also greatly enlarged. The lymphatic hypertrophy was believed by the author to have been compensatory, due to the absence of the spleen.

Hodenpyl refers to a case cited as absence of the spleen reported by E. Moroni, but was unable to obtain access to the publication. We were able to secure this publication and discovered that it related to a dog whose spleen had been extirpated and who had been observed for a period of a year after splenectomy.

Kohlhaas has recently reported a case of a woman, aged fifty-four years, who died of cerebral hemorrhage due to arteriosclerosis. All the viscera were normally situated, but no spleen was demonstrable; careful search for accessory spleens or enlarged lymph glands was unsuccessful. There was no hyperplasia of the lymphoid tissue of the intestine. The liver was small and the splenic artery came well developed from the *truncus Halleri*. The bone-marrow was chiefly of a reddish color and a small portion was yellowish. Microscopic findings were normal. At the greater curvature of the stomach and at the diaphragm a collection of fat was found in the splenic region about 5 cm. long, 2 cm. wide and 1 cm. thick; on cross-section this was found to contain a small lymph gland 1 cm. long and 0.02 cm. thick; microscopically this showed no deviation from the normal lymph gland.

Robert's case occurred in a female infant who was extremely well developed except for a rudimentary forearm, wrist and hand. The infant died three days after birth. The autopsy showed an arrested development of the stomach and absence of the spleen and omentum. The stomach had failed to undergo a primary dilatation, but retained a configuration resembling that of the duodenum.

Arnold's case occurred in a female infant who died at the age of fifteen weeks. The autopsy showed anomalies of the heart and large cardiac bloodvessels; anomalies of the pulmonary veins; anomalies of the portal vein and the ductus venosus Arantii; anomalies of both *venae cavæ* and of the hepatic veins. The spleen was missing. No changes were demonstrable.

Heusinger has collected 2 cases which are solely of historical interest. The first was reported by Lemery\* of a female infant who died at the age of eight days. Externally she was apparently normal, but at autopsy it was discovered that the entire intestinal canal was absent as well as the spleen and the liver. Occupying the normal site of these organs was a "fleshy mass as large as a

\* *Mémoires de l'Académie des Sciences*, 1704, p. 21.

child's head connected with the stomach but not with the anus, which contained arteries and veins." The second case dates back to the 16th century† and is reported as follows: "In September, 1564, a famous Antwerp merchant named Matthias Oetehius, a native of Germany, died and came to autopsy on the next following day. It was specially desired to ascertain the condition of the digestive organs, particularly the liver and spleen, for he had suffered some years previously from dropsy, a disease which is always connected with a primary or secondary pathologic condition of the liver. The expert surgeons searched under the diaphragm and the false ribs, but were unable to find any trace of these organs. This is a remarkable and unheard-of case, for the substance of the entire canal was fleshy, much firmer than muscle tissue, so as to equal nearly the firmness of heart muscle."

The case herein presented, as well as the other true cases of congenital absence of the spleen included in our collection, may be of some value in determining the importance of this organ. Although this congenital abnormality is often associated with other anatomic defects of development, it does occur as a single defect. In 9 of the cases from our collection the individuals with this anomaly reached middle life without recognizable disturbance, and one woman, who had had four normal pregnancies, died at the age of seventy-three. In our case and in the 4 other infants recorded there was apparently no hyperplasia of lymphoid tissue. In 7 of the adult cases, which were undoubtedly true cases of congenital absence of the spleen, there was no lymphoid hyperplasia, while in 2 there was definite lymphoid hyperplasia which was termed by the writers compensatory. If the lymphoid hyperplasia was in any way related to the absence of the spleen it is difficult to understand why the condition was not present in every case. In view of the fact that it was present in only 2 of the cases in our collection, it would seem that causes other than congenital absence of the spleen might have been responsible. From a review of the literature of this unusual anomaly one is justified in the conclusion that in certain individuals congenital absence of the spleen is apparently not a serious handicap.

#### REFERENCES.

- Moynihan, Sir Berkeley: *The Spleen and Some of its Diseases*, The Bradshaw Lectures, Saunders, Philadelphia, 1921.  
 Aschoff, L.: *Pathologische Anatomie*, Jena, 1911, 2d ed.  
 Ribbert, Hugo: *Lehrbuch der speciellen Pathologie*, Leipzig, 1902.  
 Ziegler, E.: *A Text-book of Special Pathologic Anatomy*, Macmillan Co., New York, 1896, p.104.  
 Delafield and Prudden: *Text-book of Pathology*, 1919.  
 Hektoen, L., and Riesman, David: *An American Text-book of Pathology*, Saunders, Philadelphia, 1901.  
 Kaufmann, Ed.: *Lehrbuch der speciellen Pathologischen Anatomie*, Berlin, 1901.  
 Adams and Nichols: *Principles of Pathology*, Lea & Febiger, 1911, 2d ed., 2, 222.

† Schenck a Graffenberg: *Obs. Med.* Basil, 1554.

Birch-Hirschfeld, F. V.: Defect der Milz bei einem Neugeborenen, Arch. f. Heilk., Leipzig, 1871, 12, 190.

Albrecht, Heinrich: Ein Fall von sehr zahlreichen über das ganze Peritoneum versprengten Nebenmilzen, Ziegler's Beiträge zur pathologischen Anatomie, 1896, 20, 512.

Sternburg, Carl: Ein Fall von Agnesie der Milz, Virchows Arch., Berlin, 1903, 173, 571.

Glinski, L. K.: Wrogowy brak sledziony (Absence of the Spleen), Przegl. lek., Krakow, 1906, 45, 707.

Riches, R. G.: A Case of Congenital Absence of the Spleen, Jour. Ment. Sci., London, 1914, 60, 639.

Rosc, F. G.: Absence of the Spleen, British Med. Jour., London, 1918, 1, 591.

Hodenpyl, Eugene: A Case of Apparent Absence of the Spleen with General Compensatory Lymphatic Hyperplasia, Med. Record, November 12, 1898.

Martin, G.: Absence de la rate, Bull. Soc. anat. de Paris, 1826, 2d ed., 1, 40.

Koch and Wachsmuth: Fehlen der Milz, Berl. klin. Wehnschr., 1879, 16, 81.

Lebby, R.: Case of Absence of the Spleen, Southern Jour. Med. and Pharm., Charleston, 1846, 1, 481-483.

Ramsey, H. A.: Gastroenteritis: Entire Absence of the Spleen, Charleston Med. Jour. and Rev., 1850, 5, 728-732.

Sachs, J. J.: Editorial, Allg. med. Central-Zeitung, February 8, 1845, 14, 89.

Jelenski: Fehlen der Milz, Berl. klin. Wehnschr., 1880, 12, 704.

Olaechca, Gonzales M.: Caso raro de ausencia del bazo, Cron. med., Lima, 1896, 13, 147.

Moroni, E., and Patellani: Osservazioni sopra un case un cane senza milza, Ann. Univ. di Milan, 1864, 187, 556-571.

Kohlhaas: Völliger Mangel der Milz, Med. Corresp.-Blatt des Württembergischen Aerztlichen Landesvereins, 1904, 74, 732.

Robert, H. L. F.: Hemmungsbildung des Magens, Mangel der Milz und des Netzes, Arch. f. Anat. Physiol. und Wissenschaftl. Medicin, 1842, p. 57.

Arnold, T.: Ein Fall von Cor triloculare biatriatum, Communication der Lungenvenen mit der Pfortader und Mangel der Milz, Virchows Arch. f. pathol. anat. in Physiol., 1868, 42, 449.

Heusinger, C. F.: Die Hemmungsbildungen der Milz, Deutsch. Arch. f. die Physiologie, 1820, 6, 17.

## DELAY IN THE TREATMENT OF CANCER.<sup>1</sup>

BY CHARLES E. FARR, M.D.,

NEW YORK.

SEVERAL years ago the statistics on delay in the treatment of cancer as seen in the first surgical or Cornell division of the New York Hospital were investigated. The results were quite startling, to say the least. Our cases were coming so late and frequently in such hopeless condition that a determined effort was made to ascertain the causes of delay.

Over 100 consecutive cases were questioned at length as to the time lost after the initial symptoms, first, before consulting a physician, and second, before entering a hospital for study and treatment. Incidentally we classified the physician's advice as good or poor, accordingly as he urged operation or counseled delay and palliation. We then classified our cases under curable, probably curable, incurable, operable and inoperable headings.

<sup>1</sup> Read before the Society for the Control of Cancer, November 7, 1921.

From these findings, meager though they were, it was at once apparent that patients procrastinate and delay for a considerable time after symptoms develop, that the physician's advice is as frequently wrong as right, that another and longer period of delay ensues before entering hospital, and that our patients finally reach us in such an advanced stage that only palliative or life-prolonging treatment is possible.

These figures, as ascertained after most painstaking investigation, were read before a scientific society in this city and offered to the leading medical journal of the country. Much to our surprise the article was rejected as casting reflection on the profession, and was rather harshly criticized. It was, however, promptly accepted and printed by the leading scientific medical journal of the country. The facts as presented were verified and substantiated by numerous writers before and since that article appeared and the popular medical journal reviewed the article at considerable length with no word of criticism.

Recently a further investigation has been made of approximately 250 additional cases, and the results are too strikingly similar to be very inaccurate. It must be remembered that the facts were obtained by many different men, working in ignorance of any desired goal, and that the tabulations and comparisons have been made by still other men, selected for their special knowledge and training, but not the responsible surgeons in charge. In this way personal bias has been, we hope, to a large degree eliminated. Inaccuracies naturally will creep into such a compilation, but we trust and believe that we have approximated the truth.

Our findings are that a delay of approximately one year occurs in the average case before adequate surgical care is sought. This means a year of delay after the development of symptoms or the appearance of a growth. Unquestionably the growth is always present for some time before symptoms or the tumor appears.

From the surgical standpoint we can state emphatically that nearly all cancers or malignant tumors are curable by the knife or other destructive measures if seen early enough. Unfortunately a considerable proportion of cases occur in deep-seated, inaccessible or non-symptom-giving locations. In such instances it is but natural that we rarely see curable cases. Mistakes in diagnosis here are also readily understood and are forgivable.

From the standpoint of our present knowledge the only hope of increasing our percentage of cures lies in obtaining cases earlier in the disease. We must shorten the time from the patient to the physician and from the physician to the hospital; possibly even we can shorten the time lost before symptoms develop by regular, systematic, complete physical examinations at not too infrequent intervals. This last idea, I fear, is quite utopian at present.



We can and must, however, reach our patients earlier, before the disease has spread beyond possible removal. The physical limits of operative removal have surely been nearly if not quite attained. Progress can come only by shortening the time preceding operation.

Education of both the laity and, I regret to say, the physicians must be pushed to the point where only wilful self-neglect can prevent timely proper treatment and a very high percentage of cures. Cancerphobia or hysteria must be avoided, of course, and grewsome discussions of neglected cases are not usually helpful. In general a calm, rational, thoughtful statement is more effectual than hysterical or alarmist appeals. After all, patients are quite reasonable in their views of health and disease if only given a fair insight into conditions.

Such methods of propaganda have been used repeatedly here and elsewhere on similar subjects, and with marked success. We firmly believe that a like success will follow sincere and earnest work in this field also. Teamwork, persistence, tact and courage will accomplish as much in our cancer work as they have in the antituberculosis campaign and in general hygiene.

Preventive treatment of malignancy offers a very hopeful field for research and practical application. We do not know the cause of cancer, but we do know what underlying conditions favor its implantation and growth. Such conditions are frequently amenable to simple and safe remedies. A trivial operation for the removal of an innocent growth, a small but persisting ulcer, a fissure, an irritated scar, etc., may prevent a severe and mutilating procedure a few years later. Even the adoption of a simple, proper diet, good hygiene and the avoidance of all excesses in eating, drinking, smoking, etc., may well be considered preventive measures against cancer. Delay in the use of the simple remedy is as foolish as in definitely established growths, or more so, as preventive cures are so infinitely safer and more sure than remedial attacks.

**Resume of Cases.** One hundred and fifty cases gave *time lost* after symptoms developed and before consulting a physician from no time to ten years. Average time, twenty-four weeks.

Time from onset of symptoms to time of consulting physician obtained in 150 cases. One of these, a slow-growing sarcoma of the arm of twenty-five years' duration, is not included in the average. Others range from no time lost to ten years; 79 consulted a physician in one month or less from the onset of symptoms. Average time, twenty-four weeks.

*Time from Consulting Physician to Time of Entering Hospital.* Obtained in 141 cases. Ranges from no time lost to nine years. With one exception all who waited over one year were cases in which the physician gave wrong advice. This was a woman with carcinoma of the cervix who waited seven years; 68 entered the

hospital within one month from the time of consulting a physician. Of these all but 3 were advised correctly. Average time, twenty-four weeks.

Time from onset of symptoms to time of entering hospital in those cases in which it was not stated when the physician was consulted, 90 cases, excluding those given above. Average time, fifty-five weeks.

#### PHYSICIAN'S ADVICE:

	Total.	Right.	Wrong.
Number curable . . . . .	43	32	11
Probably curable . . . . .	24	13	11
Incurable . . . . .	83	39	44
Operable . . . . .	74	51	23
Inoperable . . . . .	76	33	43

I wish to express my thanks to Dr. Charles L. Gibson for the privilege of publishing these statistics, as all the cases occurred in his service and were operated by him and the other members of the attending staff of the first surgical or Cornell division of the New York Hospital. I wish also to thank Dr. Morris Weeden for assistance in collecting the statistics and tabulating them.

### THE VIBRATING SENSATION IN DISEASES OF THE NERVOUS SYSTEM.

By R. T. WILLIAMSON, M.D. (LOND.).

CONSULTING PHYSICIAN, ROYAL INFIRMARY, MANCHESTER, ENGLAND.

THE "vibrating sensation" is the peculiar vibrating or trembling sensation which is felt when the foot of a *large* vibrating tuning-fork is placed firmly in contact with a subcutaneous bony prominence or surface in many parts of the body—the malleoli or the styloid process of the ulna or the sternum for example. The sensation is also sometimes described as bone sensibility or palæsthesia. Attention was specially directed to this sensation by Egger in France in 1899. Many articles have been written on the subject in foreign medical literature and a few in English literature. In previous articles<sup>1</sup> I have pointed out the value of this sensation in diagnosis, and described the method of testing it.

In this article I shall record merely my own results in clinical work, since I first commenced to test the vibrating sensation in the routine examination of the nervous cases seventeen years ago.

A tuning-fork is supplied by Messrs. Woolley & Sons, Victoria Bridge, Manchester, which is very suitable for testing this sen-

<sup>1</sup> British Med. Jour., July 20, 1907; Diseases of the Spinal Cord, London, 1908, (1911), p. 79; Jour. Neurol., August, 1911; Lancet, February 9, 1918.

sation. It is seven and one-half inches long, marked A 440, and has an oval metal foot-piece (long diameter one and one-quarter inch) attached to it. Nearly all my observations were made with this tuning-fork.

A few control observations are desirable, to see if the patient clearly recognizes the nature of the sensation before a routine examination is made.

The vibrating sensation is felt when the foot of the vibrating tuning-fork is placed over the bones of the limbs, and on the nails, on the iliac spines, sacrum, vertebral spines and bones of the thorax. It is particularly well felt over the sternum. In clinical work convenient points for testing are the styloid processes of the ulna, the inner surface of the tibia, the malleoli, the anterior superior iliac spine and the nails of the fingers and big toes. In the normal condition the vibrating sensation is always felt at these points. The sensation is not felt on the bones of the skull, but the vibrations are heard.

Normally the vibrating sensation is also felt when the foot of the vibrating tuning-fork is placed *firmly* in contact with the anterior abdominal wall.

On the anterior abdominal wall, at the level of the umbilicus, the vibrating sensation (tested with the tuning-fork I have described at the commencement of this paper) is distinctly felt in the normal condition. Also it is distinctly felt on the abdomen between the umbilicus and the thorax. On the lower part of the abdomen (below the umbilicus) it is not felt so distinctly; but by *firm* pressure of the tuning-fork the sensation is usually felt.

In 50 consecutive cases (normal individuals, or cases of mild ailments not affecting the nervous system), the vibrating sensation produced by my tuning-fork was felt on the abdomen at all the parts just mentioned, both above and below the umbilicus. But occasionally in very *stout* persons I have found that the vibrating sensation cannot be felt on the abdomen.

**Conduction of the Sensation.** The nerve fibers conducting the vibrating sensation apparently do not decussate in the spinal cord. In many cases of unilateral lesion of the spinal cord the vibrating sensation has been lost only on the side of the lesion, below the level of the disease; whilst sensation for touch, pain, and temperature have been lost on the side opposite to the lesion.

The vibrating sensation is probably not conducted upwards in the gray matter, since the gray matter has been entirely destroyed in hematomyelia at the seat of the disease, and yet the vibrating sensation has been unaffected though the sensations for pain and temperature were markedly affected. (Bing)

In one of my cases of syringomyelia (of twenty years' duration) the vibrating sensation was normal though sensation for pain and temperature were lost on the hands and arms, and the hand muscles markedly atrophied.

Bing considers it probable that the vibrating sensation is conducted upwards in the posterior columns of the white matter of the cord.

In a considerable number of cases of spinal disease, which from their symptoms have been apparently cases of combined posterolateral degeneration, I have found the vibrating sensation lost and muscular sense impaired at an early period of the disease, while other forms of sensation have been normal at this period.

#### GENERAL REMARKS ON THE VALUE OF THE VIBRATING SENSATION IN DIAGNOSIS.

1. Loss of the vibrating sensation may be a useful indication of *organic affection of the nervous system* at the earliest stage of the disease, when symptoms and signs of such lesions are very few and slight—as at the earliest stage of peripheral neuritis, tabes, and posterolateral sclerosis. Sometimes in such cases, at the earliest stages, we may detect only one or two symptoms or signs in favor of *organic* nervous disease, and if we find the vibrating sensation lost, then this is an additional indication confirming our suspicions of commencing lesion of the nervous system.

2. Loss of the vibrating sensation is frequently one of the *first indications* of *sensory* affection in many lesions of the spinal cord and in peripheral *multiple* neuritis. In such cases the vibrating sensation is often lost before other forms of sensation are affected. At a later date anesthesia to tactile and painful sensations and to temperature may occur.

3. The vibrating tuning-fork is a very delicate *test for sensation*; and if we have found the sensation normal to touch, pain, temperature, etc., before concluding that sensation is entirely unaffected, it is desirable to test the vibrating sensation; since we may, as just mentioned, find it lost though otherwise sensation is normal.

4. When *partial recovery* occurs in cases of spinal lesions which have caused marked anesthesia the vibrating sensation may remain markedly affected though other forms of anesthesia have disappeared. Thus in a case of shrapnel wound of the spine, followed by complete paraplegia and anesthesia, with bladder symptoms, after laminectomy marked improvement followed. Two years later the patient was able to walk though the legs were spastic; the bladder symptoms had disappeared and sensations of touch, pain and temperature were felt distinctly; but the vibrating sensation was still lost on the legs.

In hemianesthesia from cerebral lesions we find that when recovery occurs the vibrating sensation returns *before* tactile sensation. Thus in a case of hemiplegia and hemianesthesia of sudden onset (probably due to hemorrhage), at first sensation, to the vibrating

tuning-fork and to all forms of sensibility was lost on the left side. At a later date, when marked improvement had occurred, the vibrating sensation and also painful sensations were felt on the left side; but sensation to touch was lost. This is thus the opposite of the condition in many cases of spinal anesthesia.

In spinal anesthesia the vibrating sensation is often the first to be affected and the last to recover; while in cerebral anesthesia the vibrating sensation may be the least affected, and if affected it may recover before tactile anesthesia. I have never met with a case of loss of the vibrating sensation alone in a cerebral lesion.

5. Certain diseases of the spinal cord affect only the motor parts of the cord. Anesthesia to any form of sensation would therefore exclude such diseases, or at least show that the pathologic changes had spread to the parts of the cord in which sensory structures are situated. Hence the detection of any affection of sensation is of great diagnostic value. But at first sensation to touch, pain and temperature may be normal; and until we test the vibrating sensation we may consider that the disease is localized entirely in motor parts. If, however, we find that the vibrating sensation is lost we have then an indication that the disease has affected sensory parts of the nervous system; and we can therefore exclude at once all diseases which are known to affect only motor parts of the nervous system. Thus in cases which we suspect to be anterior poliomyelitis or amyotrophic lateral sclerosis, we may exclude these diseases if we find the vibrating sensation lost.

6. The vibrating sensation is also sometimes of service in the diagnosis between paraplegia due to organic disease and paraplegia due to hysteria, functional affections or malingering. In any case of paralysis of the legs, if we find that the vibrating sensation is lost, while other forms of sensation are felt, and the patient persists in this statement in spite of suggestions to the contrary, then I think that hysteria or functional affection is very improbable. In paraplegia due to hysteria or functional affection or malingering my experience has been that if the vibrating sensation is lost other forms of sensation will also be affected, or that by suggestion, through the form of the question, the patients will state that they are affected.

7. The loss of the vibrating sensation on the abdomen may be of service in indicating the upper limit of a spinal lesion in traumatic and other spinal affections when other forms of sensation are not affected. Thus the vibrating sensation may be lost on the abdomen up to one inch above the umbilicus, while it may be felt on the abdomen above this level. This would be a guide to the level of the spinal lesion. (In testing, the foot of the tuning-fork should be pressed very firmly against the abdominal wall.)

THE DIAGNOSTIC VALUE OF LOSS OF THE VIBRATING SENSATION  
IN VARIOUS NERVOUS DISEASES.

In certain diseases of the nervous system affecting motor structure only the vibrating sensation is always felt. Thus I have never found it lost, even at an advanced stage of the disease, in cases of amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, acute and chronic anterior poliomyelitis (in the infant or adult) and paralysis agitans. Also I have never found it lost in pseudohypertrophic paralysis, idiopathic muscular atrophy, neurasthenia (unassociated with hysteria). Loss of the vibrating sensation would therefore be a strong point against the diagnosis of the affection just named.

The following remarks will indicate the value of the vibrating sensation in the differential diagnosis of various diseases.

At the earliest stage of *multiple peripheral neuritis*, from various causes, loss of the vibrating sensation may often be detected before loss of any other form of sensation. At this earliest period often the chief symptoms are pains in the legs and muscular tenderness, and it is often difficult to decide if these are due to commencing *organic* disease or not. On examination at this earliest period no anesthesia to tactile impressions, pain or temperature may be detected, and though the patient may complain of weakness in the legs, no definite paralysis or paresis may be detected. Also the knee-jerks may, at this *earliest* period, be still obtained. But in these cases two symptoms may be frequently detected which clearly indicate commencing organic disease; these are loss of the tendo-Achillis reflexes and loss of the vibrating sensation. At a later period in these cases the knee-jerks disappear and muscular paralysis and loss of other forms of sensation may be detected. We have thus four very early signs of *multiple peripheral neuritis*: (1) Pain in the legs; (2) tenderness of the muscles; (3) loss of the tendo-Achillis jerks; (4) loss of the vibrating sensation.

These remarks apply to alcoholic neuritis, arsenic neuritis, diabetic neuritis and multiple neuritis of other forms.

*Nervous Complications in Diabetes Mellitus.* In diabetes pains in the legs and tenderness of the calf muscles are not infrequent symptoms and are usually attributed to slight diabetic multiple peripheral neuritis, but paresis or paralysis is very rare. In these diabetic cases we often find that the tendo-Achillis reflexes are lost, and less frequently the knee-jerks also, and that the vibrating sensation is lost, though other forms of sensation are felt. In these very early cases of nervous complications, at first, only one of these symptoms may be present. Thus pain may be the only nervous symptom or loss of the tendo-Achillis reflexes or loss of the vibrating sensation, while later all these three symp-

toms may be present and additional symptoms may develop. I have found occasionally, in diabetic patients, that the vibrating sensation has been lost on the legs, even when the knee-jerks and tendo-Achillis reflexes have been present and the patient has not suffered from pain in the legs except cramp in the calf muscles at night. In other early cases and much more frequently, two of the symptoms just named have been present—pain and loss of the vibrating sensation or loss of the vibrating sensation and loss of the tendo-Achillis reflex or pain and loss of the tendo-Achillis reflex. Hence we may say that in diabetes mellitus the vibrating sensation is occasionally lost on the legs (malleoli and inner surface of the tibia) when other nervous symptoms are absent or slight. But the additional early symptoms just mentioned usually develop soon and others may develop later.

In 100 consecutive cases of diabetes I found the vibrating sensation was lost on the legs (malleoli and inner surface of the tibia) in 18 cases.

In a few of the cases of diabetes presenting these nervous symptoms usually described as "neuritis," pathologic examination has revealed changes in the peripheral nerves, but not always. I have found (in a case which I have recorded) that the peripheral nerves showed no definite microscopic changes (in the fibers examined); the posterior nerve roots, however, showed marked degeneration at their entrance into the cord directly after passing through the pia mater.

Loss of the vibrating sensation is often a useful sign in the differential diagnosis of multiple peripheral neuritis from acute anterior poliomyelitis affecting both legs, since in the later affection the vibrating sensation is not lost.

The symptom was of particular service in a case which I saw at the end of the war period. A man had been invalided home from France; paralysis of the legs had developed and slight paresis of the arms. The knee-jerks and tendo-Achillis reflexes were lost; the bladder was unaffected. Sensation to touch, pain and temperature could be felt. A diagnosis of spinal-cord affection and a very unfavorable prognosis had been given previously. On examination anterior poliomyelitis appeared very probably, as pain and muscular tenderness in the limbs had not been prominent symptoms, though both were present. But three symptoms were against the diagnosis of anterior poliomyelitis (subacute or acute):

(1) The vibrating sensation was lost on the legs; (2) the paralysis in the arms was more similar in its distribution to that of peripheral neuritis than to anterior poliomyelitis; (3) The intercostals were not paralyzed, though both arms and legs were affected.

Chiefly on account of the loss of the vibrating sensation I gave a diagnosis of multiple peripheral neuritis and a favorable prognosis. In the course of many months complete recovery occurred.

In *sciatica* and in *primary brachial neuritis* I have never detected loss of the vibrating sensation.

In lesions of a *single peripheral nerve* or a *peripheral nerve trunk* I have never found the vibrating sensation lost, when tested with the tuning-fork I have described in this article, even though other forms of sensation (to touch, pain or temperature) have been affected. Occasionally I have found the vibrating sensation much diminished but never lost, and in most cases it is felt quite well. This is a point sometimes of service in differential diagnosis. In a case of localized paralysis (whether other forms of sensation are lost or recognized), if the vibrating sensation is *completely* lost a lesion of a *single peripheral nerve* or *nerve trunk* can be excluded as the cause of the paralysis.

In *acute anterior poliomyelitis* of the infant and adult the vibrating sensation is unaffected. This fact is occasionally of much service, as already mentioned, in the diagnosis between multiple peripheral neuritis and acute anterior poliomyelitis causing paralysis of both legs. Usually the pain and muscular hyperalgesia in peripheral neuritis is so pronounced that the diagnosis is easy, but we have to bear in mind that occasionally in acute anterior poliomyelitis at first some pain and muscular tenderness may occur, and occasionally in peripheral neuritis these two symptoms are not very pronounced at first. The loss of the vibrating sensation would be in favor of multiple peripheral neuritis and would show that sensory structures in the nervous system were affected, and that the case was not one of acute anterior poliomyelitis.

In the diagnosis between acute anterior poliomyelitis and *acute disseminated myelitis* or *acute myelitis* the vibrating sensation is helpful. All three diseases may cause paralysis of both legs, and at first sensation to touch, pain and temperature may be normal in acute disseminated myelitis or acute myelitis, as well as in acute anterior poliomyelitis, but in the two former affections the vibrating sensation is often lost. The vibrating sensation may then be of much service in the diagnosis; if lost, acute anterior poliomyelitis may be excluded.

I have found the vibrating sensation of much service in the diagnosis of acute anterior poliomyelitis from the two affections just named and from other spinal diseases, and have recorded cases.

In chronic (and subacute) anterior poliomyelitis the vibrating sensation is not lost, and this fact is occasionally of service in the differential diagnosis of these affections from multiple peripheral neuritis and other spinal cord diseases. Thus in two of my cases of slowly developing paralysis of the legs, with loss of the tendo-Achillis reflexes, the fact that even the vibrating sensation was unaffected (as well as other forms of sensation) was a point, along with others, in favor of chronic anterior poliomyelitis, and enabled



one to exclude many other diseases which might have produced similar motor symptoms.

Primary *lateral sclerosis* is certainly an *extremely rare* disease and can be excluded in any cases in which the vibrating sensation is lost. In all cases which appear to be instances of this rare affection the vibrating sensation should be tested before the diagnosis is given. In one of my cases of spastic paraplegia the fact that the vibrating sensation was present at the end of twenty years was one point, along with others, in favor of the diagnosis of primary lateral sclerosis. (In this case the bladder and rectum had not been affected, no wasting of hand muscles had developed, sensation was unaffected and no signs could be detected of affection of any part of the spinal cord except the lateral pyramidal tracts even at the end of twenty years.) In another case of spastic paraplegia of fifteen years' duration loss of the vibrating sensation, slight nystagmus and occasional diplopia were points against primary lateral sclerosis and in favor of disseminated sclerosis.

In *amyotrophic lateral sclerosis* the vibrating sensation is not lost even at the terminal stage of the disease. In any case of suspected amyotrophic lateral sclerosis, loss of the vibrating sensation would be evidence against this diagnosis.

In many cases which have presented the symptoms of *combined posterolateral spinal degeneration or sclerosis (ataxic paraplegia)* I have found the vibrating sensation lost at a very early stage of the disease. At first the symptoms have been chiefly slightly impaired coördination (slight ataxia), Babinski reflexes, impaired muscular power and loss of the vibrating sensation, while other forms of sensation have been felt. Later ankle-clonus and spastic condition of the legs have developed. In some of these cases at a later period sensation to touch, pain and temperature have been much affected. At the earliest stage the loss of the vibrating sensation is a valuable sign of commencing organic disease and is often of much service in diagnosing these cases from functional affections or malingering. I have recorded such cases elsewhere. I may mention one, however, which was of special interest:

A man consulted me in January, 1917, complaining of weakness and heaviness in the legs and slight unsteadiness in walking. He was called up for military service and considered that he was unsuitable on account of these symptoms. The question of malingering or neurasthenia had to be considered. I examined him very carefully, but could then detect no signs of organic disease. He was able to walk alone and showed only very slight unsteadiness, but complained that his legs felt heavy and weak.

In May, 1917, I again examined him and then detected (1) that the gait was slightly ataxic; (2) that the vibrating sensation was lost on the legs, but other forms of sensation were unaffected; (3) that the plantar reflexes were difficult to obtain, but several

times a Babinski reflex was obtained. No other signs of organic disease could be detected, but from the symptoms just named I gave a diagnosis of commencing spinal disease.

In November, 1917, I again examined him. Then the chief symptoms were: (1) definite paresis of the legs; (2) ataxic gait; (3) slight spastic condition of the legs; (4) knee-jerks increased and ankle-clonus and Babinski reflex on each side; (5) muscular sense greatly impaired; (6) vibrating sensation lost on both legs but other forms of sensation recognized. At this period there was no doubt as to the diagnosis of organic spinal disease, and posterolateral sclerosis or degeneration was very probable; but at the earlier examination in May the only definite indications of organic disease were the loss of the vibrating sensation and the occasional Babinski reflex.

I have had many spinal cases in which at first the chief symptoms have been: (1) loss of the vibrating sensation while other forms of sensation have been normal; (2) slight incoördination in walking or affection of the muscular sense in the legs, and (3) Babinski plantar reflexes. These cases have usually developed later marked symptoms of posterolateral degeneration (or sclerosis) ataxic paraplegia.

In *disseminated sclerosis* sensation is very often reported as normal, and this is probably correct as regards sensation for touch, pain and temperature; in other cases these sensations are definitely affected. But if the vibrating sensation be tested it will be found to be lost in a large number of cases of disseminated sclerosis, though other forms of sensation are felt distinctly.

In many cases of disseminated sclerosis I have found the vibrating sensation lost on the legs; in some cases lost on the lower half of the abdomen and also on the legs; in others on the whole of the abdomen and the legs. In a few cases the vibrating sensation has been lost on the middle or lower part of the abdomen but not on the legs and chest. In one case the vibrating sensation was lost only on one-half of the lower two-thirds of the abdomen.

The abdominal and epigastric reflexes are usually lost when the vibrating sensation is not felt on the abdomen in disseminated sclerosis.

In atypic cases of disseminated sclerosis, when the symptoms are chiefly those of spastic paraplegia, the case may closely simulate primary lateral sclerosis. But if we find that the vibrating sensation is lost this symptom would exclude primary lateral sclerosis and would be one point in favor of disseminated sclerosis. I have found this symptom sometimes of much service in diagnosis.

My own experience has been that in disseminated sclerosis, if sensation is impaired, *by far the most common form of impairment is loss of the vibrating sensation*, while other forms of sensation are felt; and that this condition is met with in a large proportion of the cases.

In *tabes dorsalis* at the very early stage the vibrating sensation is sometimes lost on the legs though other forms of sensation (to touch, pain and temperature) are normal. Hence in the diagnosis of *tabes* at the earliest stage, when the symptoms are few and slight, loss of the vibrating sensation may be of diagnostic value as additional evidence in favor of this disease.

In *hematomyelia* when sensation for pain and temperature have been markedly affected the vibrating sensation has been found unaffected, though the gray matter has been destroyed at the seat of the disease. (Case recorded by Bing.)

In a case presenting typical symptoms of *syringomyelia* of twenty years' duration I found the vibrating sensation unaffected, though sensation for pain and temperature were lost.

In the various forms of *spinal syphilis*, and specially in Erb's chronic form—*syphilitic spastic spinal paralysis*—the vibrating sensation is sometimes lost on the legs at the early period before other forms of sensation have become affected.

In *compression myelitis* due to *spinal caries* at the earliest period often no anesthesia to touch, pain or temperature can be detected. In addition to pain in the back and root pains there may be only slightly impaired muscular power in the legs and slight changes in the reflexes; yet at this stage the vibrating sensation is often lost on the legs and anterior iliac spines, being then the only form of sensation impaired.

In *spinal meningeal tumor* loss of the vibrating sensation may be the first form of sensory loss, *i. e.*, at the early stage we may find loss of the vibrating sensation on the legs while sensation to touch, pain and temperature are then unaffected. We have often, in the development of the symptoms of spinal meningeal tumor, a brief period at first in which paresis or paralysis of the legs is detected, but the reflexes are normal. The knee-jerks are normal and no ankle-clonus and no Babinski reflexes can be detected, and sensation of touch, pain and temperature are felt readily. In such cases the question of hysteria or functional affections may arise. But at this period we may find the vibrating sensation lost on the legs, and this would then be a sign in favor of organic disease. In these cases a Babinski reflex is soon obtained, ankle-clonus develops and anesthesia to touch, pain and temperature is afterward detected below the lesion.

In *compression myelitis from injuries* to the spine, and in other forms of traumatic lesion of the spinal cord, the upper limit of the anesthesia produced often indicates the localization of the lesion.

In *incompletely transverse lesions*, however, the sensation for touch and pain may not be lost, but the vibrating sensation alone may be lost below the lesion (on the bones of the legs and on the abdomen). On the skin of the abdomen the vibrating sensation may then be used to determine the upper limit of the sensory dis-

turbance and may thus be of localizing value (as pointed out by Dr. Gordon Holmes.<sup>1</sup>)

In *cerebral* diseases I have never found the vibrating sensation affected alone or before other forms of sensation. When other forms of sensation are lost the vibrating sensation may also be lost, but it appears to be affected to a less extent than sensation to touch, pain or temperature. Also in recovery from anesthesia due to cerebral disease the vibrating sensation appears to return before other forms of sensation.

In *hysteria*, *functional affections*, *neurosis*, *neurasthenia* and *malinger*ing I have never found the vibrating sensation lost when other forms of sensation were unaffected or unaffected after suggestion. In any case of paresis or paralysis of the legs, if the vibrating sensation is lost while other forms of sensation are recognized readily, and if the patient persists in this statement in spite of suggestions to the contrary by the wording of the questions, then hysteria or malingering is very improbable. In these conditions if the vibrating sensation is lost other forms of sensation will also be affected, or after suggestion, by the form of the questions, the patient will state that they are affected.

In a case of *localized paralysis* in a limb, if the vibrating sensation is lost and other forms of sensation are felt, or lost, a lesion of a peripheral nerve or nerve trunk can be excluded as the cause of the paralysis. In a case of localized paralysis, if the vibrating sensation is lost and other forms of sensation are recognized, and the patient persists in this statement in spite of suggestions to the contrary, then hysteria or malingering is very improbable.

In any case of *hemianesthesia*, if the vibrating sensation is not felt when the foot of the vibrating tuning-fork is placed on the edge of the sternum on the side of the tactile anesthesia, but felt when placed at a corresponding point on the other side, the case is one of hysteria or functional disease or malingering. (When the vibrating sensation is felt when the vibrating tuning-fork is placed on either side of the sternum no conclusion can be drawn from this fact as to the diagnosis.) In cases of hemianesthesia due to organic disease, if sensation is impaired over the sternum at all, when the tuning-fork is placed over the half of the sternum on the anesthetic side the vibrations would be transmitted across to the other half of the sternum and would at least be felt there. In all cases examined by myself, if due to organic disease, the tuning-fork vibrations have been felt when the tuning-fork has been placed on either half of the sternum.

The vibrating sensation may also be of service in a similar manner in the diagnosis between functional and organic *anesthesia limited to a portion of a limb*, as I have elsewhere described in the following words:<sup>2</sup>

<sup>1</sup> British Med. Jour., November 29, December 4 and 11, 1916.

<sup>2</sup> Rev. Neurol. and Psych., November and December, 1918.

"If the anesthesia is limited to a portion of a limb or one portion of the body, and if a long bone such as the tibia, ulna, femur or sternum is situated partly in the anesthetic area and partly in the non-anesthetic area, then the following test is occasionally of diagnostic service: If we find that the vibrating sensation is not felt *anywhere*, when the foot of a large vibrating tuning-fork is placed on a subcutaneous part of the bone just within the area of anesthesia, but the vibrations are felt when the foot of the vibrating tuning-fork is placed on the subcutaneous part of the bone just outside the area of cutaneous anesthesia, then the case is one of functional anesthesia (hysteria, malingering or 'idea' anesthesia). (If the vibrating sensation is not felt at both these points, no conclusion can be drawn from this symptom alone.)

"In the normal condition, when the foot of a large and suitable vibrating tuning-fork is placed on the subcutaneous surface of one end or one part of a bone, the vibrations are transmitted all over the bone, and are felt, though with diminished intensity, at distant parts of the bone. Hence if the foot of the vibrating tuning-fork is placed on the bone just within the limit of the anesthesia, though the vibrating sensation may not be felt at that point, the vibrations will be transmitted to other parts of the bone and should be felt there if the vibrating sensation of the other part or parts is not lost. If we find, therefore, that the vibrating tuning-fork is felt just outside the limit of the anesthetic area, this indicates that the vibrating sensation is not lost in the bone at this point, and therefore the transmitted vibrations should be felt *there* when the foot of the vibrating tuning-fork is placed within the anesthetic area."

In a case of *pernicious anemia* I have found the vibrating sensation lost though no other indications of lesion of the nervous system could be detected, but the patient complained of a sensation of numbness in the legs. (Probably spinal changes were commencing.)

In cases of *gangrene* of the toes associated with diabetes mellitus, and in cases of *perforating ulcer* of the foot associated with tabes or diabetes mellitus, we often find the vibrating sensation lost on the legs. The loss of this sensation is then due not to the gangrene or perforating ulcer but to the diabetes or tabes.

The remarks which I have made are sufficient to show the value of the vibrating sensation in the diagnosis of nervous diseases and to indicate that it is desirable to test this sensation in all cases in which a detailed examination of the nervous system is undertaken.

The following are common combinations of early signs of organic disease:

1. Loss of the vibrating sensation on the legs, slight incoördination, Babinski reflexes. (Later signs of ataxic paraplegia or combined posterolateral sclerosis or degeneration.)

2. Loss of the vibrating sensation on the legs or on the abdomen and legs or on the abdomen only. Babinski reflexes, loss of abdominal reflexes. (Later signs of disseminated sclerosis.)

3. Girdle pains, often for a long period; then loss of vibrating sensation on the legs, with Babinski reflexes. (Later signs of compression myelitis from tumor of the meninges or vertebræ.)

4. Loss of the vibrating sensation, loss of the tendo-Achillis reflexes, pain in the legs. (Later loss of knee-jerks and other symptoms of peripheral *multiple* neuritis.)

---

## THE RELATIONSHIP BETWEEN CENTRAL AND PERIPHERAL INVOLVEMENT OF THE CRANIAL NERVES.\*

BY ERNEST SACHS, M.D.

PROFESSOR OF CLINICAL NEUROLOGICAL SURGERY, WASHINGTON UNIVERSITY MEDICAL SCHOOL, ST. LOUIS, MISSOURI.

IN the brief time assigned to me it is obviously impossible to deal with all the symptoms caused by endocranial involvement of the cranial nerves. I have therefore selected for consideration some of the symptoms of cranial nerve involvement which present unusual difficulties in diagnosis and about which our knowledge is still incomplete. I propose to confine my remarks to the first, second and eighth nerves and those portions of the fifth and ninth nerves which are concerned with taste. In other words, I am going to consider the cranial nerves that control the special senses in which you are particularly interested.

The various studies that have been carried on to locate the cerebral centers controlling the special senses have cleared up many points that have hitherto been shrouded in mystery, but there still remain a goodly number on which light needs to be thrown. But whether the loss of one of these functions is due to destruction of the end-organ, the cerebral pathways or center is still often most perplexing. You see a large number of such cases where we see one. If it would be possible to create a uniform method of study of all such cases, then a Gunn, a Helmholtz or a Hughlings-Jackson, or even a lesser light, might take this vast material, which both in quality and quantity has never hitherto been dreamed of, and cull from it most valuable information. The study of these special senses is beset with unusual difficulties, for here we are dealing with sensory phenomena which are difficult to throw light upon by any experimental observations on animals, since obviously

\* Read before the Section on Instruction of the American Academy of Ophthalmology and Otolaryngology, Philadelphia, October 19, 1921.

indirect methods must be employed to determine a disturbed function in an animal.

The anatomist has quite outstripped the physiologist in this field, for the course of the fiber connections for the most part is quite well known. There are three methods of studying the physiology of these special senses in animals. The first method consists in destroying a portion of the brain and noting whether the animal no longer reacts to a certain sensory stimulus.

In the second method similar observations are made on specially trained animals. An animal is trained to do a certain thing, let us say raise its right forefoot when a certain odor is presented to it, and then after some lesion has been produced one notes whether the animal still does this. This method has been carried out to a high degree of perfection by Kalischer, but there are inherent dangers in the method which throw doubt on its value. It presupposes, it seems to me, that these artificially developed reflexes are so firmly fixed in the animal's mind that a severe trauma, as removal of part of the cerebral cortex, will not influence them unless the function that is being studied is disturbed. Yet forgetfulness has at all times and in all ages been characteristic even of the human race. Even Homer records that the mere eating of the lotus fruit could produce complete amnesia. The pathway by which an artificial reflex is carried out can certainly be more readily inhibited than can the pathway that an animal has always possessed, as in the case of the sucking reflex or the bladder reflex. Therefore, when a certain stimulus does not lead to the reaction to which an animal has been trained, though it suggests that the stimulus is not appreciated, there is always a lurking suspicion which this method of investigation can never dispel that the acquired habit has been lost as a result of the trauma. In man after a severe cerebral injury it is a very common experience to find that the patient's memory for events of all sorts just preceding the accident is lost for weeks and often months. If this is true in man there is every reason why it should also be true in animals.

The third method has been to determine the presence or absence of a salivary reflex when a strong sensory stimulus is produced. This reflex can be elicited with the greatest ease in experiments on monkeys when the anesthetic becomes light, as I have been able to demonstrate to my own satisfaction repeatedly. It therefore makes me feel that the method is too unreliable to be seriously considered.

Up to the present time, therefore, the results of such investigations on animals, many of them very elaborate and careful, have had the serious handicap of uncertainty. I am convinced that the next real advances will be made when accurate clinical observations are subjected to the acid test by research students.

The more careful study and interpretation of subjective sensations, which of course can only be done on human beings, it has seemed to me would lead to advances in this field. By subjective sensations is meant those peculiar phenomena in which a patient complains of certain sensations which are not susceptible of other proof than the patient's assertion. Thus he may say he thinks he smells certain odors when there is nothing around to produce them, or he hears or sees or tastes something when the stimulus to produce these is not present.

The difficulties of the problem are nowhere better illustrated than in the olfactory mechanism. So little is really known on this subject that von Bechterew in his three volumes on the functions of nerve centers devotes but ten pages to the entire subject.

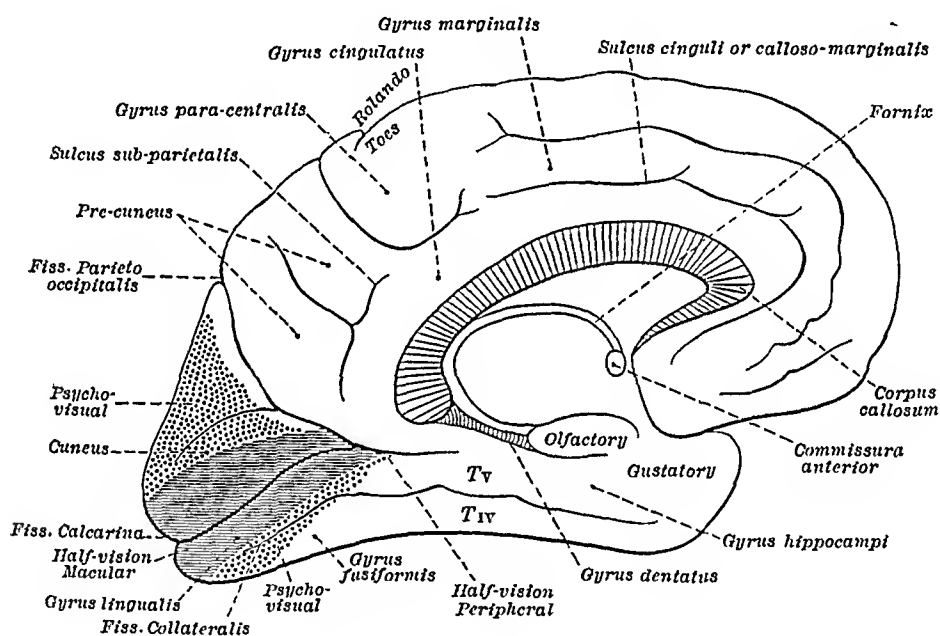


FIG. 1.—From Purves Stewart.

It is now quite generally conceded that the olfactory mechanism after leaving the olfactory bulbs at the base of the frontal lobes passes *via* the fornix to the gyrus uncinatus and pyriformis of the hippocampal lobe (Fig. 1). There is another group of fibers, the fibers of Lancisi, less well developed but of considerable size, which belongs to this mechanism. Our interest lies in differentiating smell disturbances if possible when they occur in these various regions. A lesion in the nose causes loss of all forms of smell, and so does a lesion in the olfactory pathways in the nervous system, unless the lesion, instead of being destructive, is irritative in character. This can be caused by an inflammatory process or merely when there is pressure on the hippocampal lobe; in such a case the patient experiences subjective sensations of smell. I have



believed that the presence of a subjective sensation of smell always means a hippocampal lesion, yet rhinologists have observed patients with this symptom with apparently only a nasal lesion. I know of no instance, however, in which such a case with the lesion supposedly in the nose has had its brain studied. Such studies would be essential to clear up this point. Is the loss of smell resulting from a nasal lesion the same as from a central lesion? Is the recognition of certain odors more inhibited in a peripheral lesion than in a central one? Does unilateral loss of smell occur with a lesion in one hippocampal lobe? How is the power to perceive an odor without the ability to name it to be interpreted? Do fluctuations in the sense of smell occur with lesions in one portion of the tract and not in the other?

Most of these questions still need further elucidation. A lesion in the nose when it leads to loss of smell usually causes complete bilateral loss. On the other hand, a destructive lesion of the gyrus pyriformis is said, at least in animals, to cause loss of smell in the nostril of the same side and some diminution of smell on the opposite side. The examination of the sense of smell is so uncertain even on intelligent human beings that tests on animals even by such eminent observers as Ferrier, Luciani and von Bechterew cannot be relied upon, especially when the latter claims to have noted unilateral *diminution* of the sense of smell in a dog. That the uncinate gyrus at least at times controls smell on both sides is illustrated by a case on which I was able to make careful tests (Fig. 2). No sensation of smell was present on either side, yet the lesion was only in one hippocampal lobe and his peripheral mechanism seemed normal.

The presence of subjective sensations of smell is evidence of a cortical lesion, the so-called uncinate fits that are most frequently encountered in pituitary disease, but there our knowledge ends. We are unable to distinguish a lesion of the olfactory bulbs from a lesion in the nose, nor do we know how to recognize a lesion of the fornix or the fibers of Lancisi.

A further point of great interest is how much reliance we may put on the ability of a patient to name odors as contrasted with his ability to recognize the presence of an odor without naming it. Does the naming of an odor constitute more of a mental process, and if it does, is this controlled by a different portion of the brain? If there is any occupation in which the olfactory sense is specially trained as tasting is in tea-tasters or the ear in a musician, the study of a pathologic lesion in the hippocampal lobe in such a patient might be of tremendous value.

The known facts in regard to taste are no more certain; in fact, the incontrovertible evidence is practically negligible. Even the peripheral portion of the mechanism offers difficulties of interpretation, and one wonders what the biologic significance of having

two peripheral pathways for carrying impulses of taste may be; the important role that taste plays in digestion may be the cause of this extensive peripheral nerve supply.

The taste fibers passing through the fifth nerve and those in the ninth carry the same sensations, and any differentiation is controlled in the cerebral portion of the pathway. About the ultimate cerebral terminations of the fibers there is much uncertainty, and in this instance the doubt is anatomic as well as physiologic. One group of observers believes the cortical center for taste lies in the hippocampal lobe nearer the convexity of the hemisphere (Fig. 1), while another group believes the center lies in the operculum near the motor center which controls the movements of the tongue and lips (Fig. 3). The most important investigation of this subject has been carried out in von Bechterew's laboratory by several of his assistants. A critical analysis of their work inevitably leads one to the conclusions that testing taste on animals is very



FIG. 2.—The tumor was an infiltrating glioma located at "A."

uncertain. These investigators have concluded that there is more or less marked diminution in the sense of taste and that this *diminution*—not loss, I would have you note—is more marked on the side opposite the lesion than on the same side. Such fine distinctions I feel confident are not possible in animals, since at least in my experience they are hardly ever possible in human beings. Furthermore, all taste tests to be reliable should be carried out with the patient's tongue protruded, since substances diffuse so rapidly on the moist tongue. In these experiments the test substances were introduced with a pipette on one or the other side of the tongue. The clinico-pathologic evidence is excessively meager, so that we are inevitably led to the conclusion that further studies on the sense of taste are urgently needed if we are to be able to make use of these sensory phenomena in more accurately determining the significance of disturbances in taste.

I have thus far dealt with the two special senses about which we know the least. Fortunately our knowledge of sight and hearing

is far greater; in fact, the mass of evidence, both experimental and pathologic, is so huge that a clear analysis of all this work would take much longer than is possible here.

I shall therefore select certain phases which bear particularly on the question of differentiating peripheral from central lesions.

1. Disturbances of ocular movements.
2. Disturbances of vision.

The movements of the eyes are controlled by the third, fourth and sixth nerves and their nuclei in the pons. Movements of the eyes can also be brought about by stimulation or destruction of the anterior corpora quadrigemina, that portion of the optic thalamus known as the pulvinar, the occipitotemporal region of the cortex and a center in the second frontal convolution (Fig. 4.).

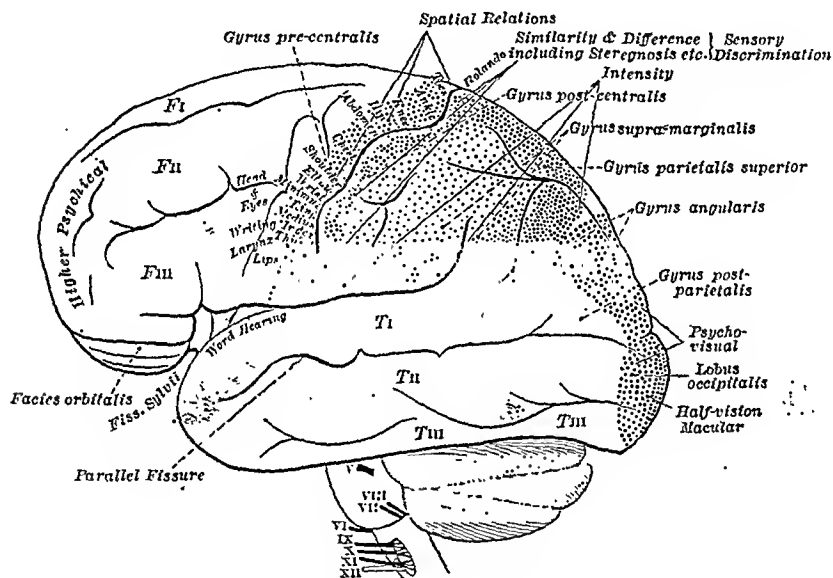


FIG. 3.—From Purves Stewart.

Though we are dealing here with motor phenomena these movements form such an intimate part of the visual mechanism that I feel justified in considering them:

The characteristic picture of an ophthalmoplegia needs no consideration here. The differentiation of irritative lesions of the peripheral nerves from lesions of the cerebral regions just mentioned, offer however, a real problem.

Experimentally it has been shown that stimulation of the anterior corpora quadrigemina brings about a spasm of accommodation and conjugate deviation of both eyes to the opposite side. This conjugate deviation may be to the side, upward or downward, depending on which portion of the quadrigeminal body is stimu-

lated; marked convergence of both eyes can also be brought about by stimulation of this region. All these movements can also be produced by stimulating the occipital cortex, the frontal region and the optic nerve, but if the corpora quadrigemina are destroyed stimulation of the occipital lobe no longer produces these movements, though they still can be produced by stimulation of the frontal center.

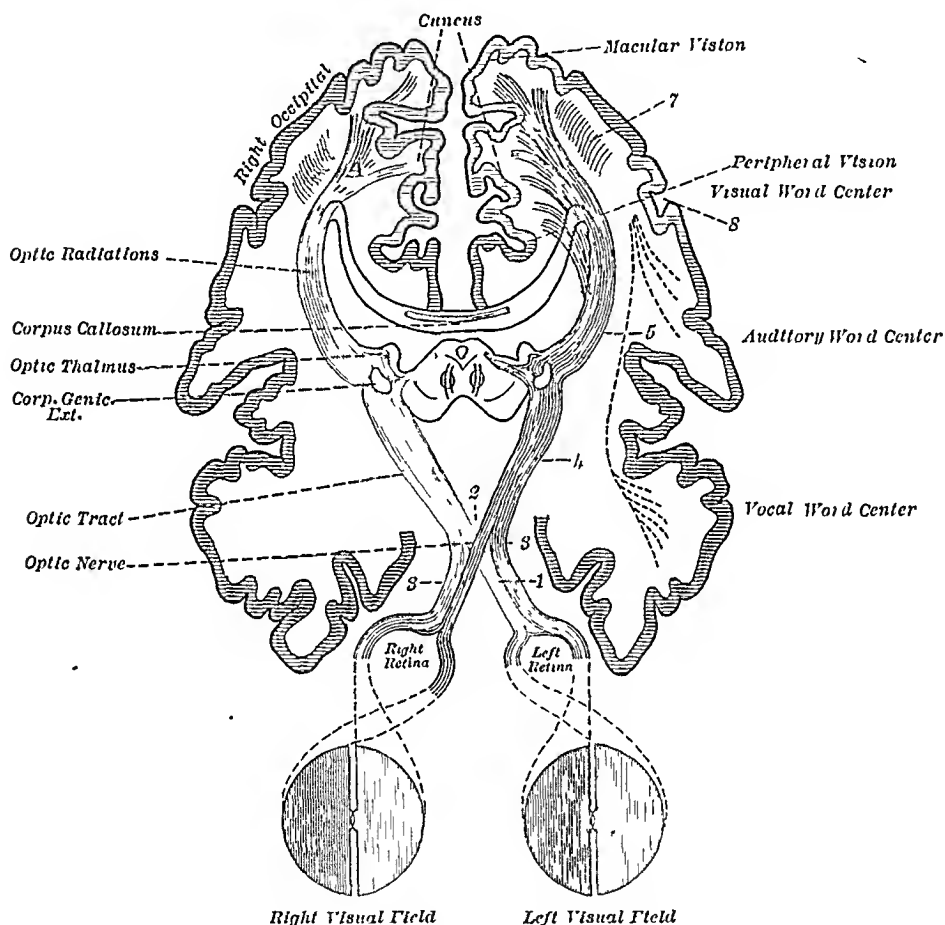


FIG. 4.—From Purves Stewart.

This is clear evidence to physiologists that the corpora quadrigemina are merely reflex centers and not primary centers, but this explanation does not materially help the clinician to differentiate lesions of these various regions.

Is our knowledge of these various regions adequate to enable us to recognize when they are diseased, and if so what are the salient points? That most accurate differentiation would be of great value is illustrated by the common example of conjugate deviation of the eyes which is noted in cerebral hemorrhage due to vascular disease and cerebral hemorrhage due to trauma.

When the symptoms are compared in parallel columns the dif-

ferences seem (see table) quite clear, but when applied to a particular clinical case the problem is by no means simple. For example, the

Frontal.	Occipital lobe.	Anterior corpora quadrigemina.	Optic nerve.
Conjugate deviation of the eyes. Vision intact.	Conjugate deviation of the eyes. Homonymous hemianopsia or homonymous visual impressions.	Conjugate deviation of the eyes. Homonymous hemianopsia.	Partial, complete or no ophthalmoplegia depending on involvement of 3d, 4th or 6th nerves.
Weakness or twitching of face of opposite side.	No motor involvement.	Hemiparesis or no motor disturbance depending on size of lesion.	Blindness of one eye or contraction of field depending on degree of involvement of nerve.
Pupillary reflexes undisturbed.	Pupillary reflexes undisturbed. Cortical blindness (Seelenblindheit).	Pupillary reflexes abolished.	No motor involvement. Pupillary reflexes abolished if blindness complete.

significant differential point between a frontal and occipital lesion is a field defect, but so often unconsciousness is present to thwart one in distinguishing frontal from occipital conjugate deviation. Experimentally Gerver, in Bechterew's laboratory, observed that ocular movements were more readily produced by frontal-lobe stimulation than by stimulation of the occipital lobe. How to make use of this interesting experimental observation in a clinical case I am at a loss to know. There are a few associated symptoms that may be helpful in clarifying these confusing pictures. If, associated with conjugate deviation, there are irritative motor phenomena, Jacksonian convulsions, it is more probable that the conjugate deviation arises from the frontal region rather than from the occipital region, since the frontal center lies so near the motor cortex. On the other hand, visual hallucinations would point rather to an occipital lesion, while the presence of high temperatures must always suggest the possibility of a ventricular involvement and consequently a lesion of the corpora quadrigemina, which protrude into the ventricle. The evidence of so-called heat centers in the brain is not to my mind conclusive in spite of the extensive studies of Barbour. In some unpublished experiments carried on in my laboratory by Captain Philip Green the evidence was not so positive that we felt convinced of the existence of a heat center or of its definite location. In other words, we are in the strange situation that though knowing quite accurately the functions of some of these centers we are often unable to determine by our present methods which center is involved.

The act of vision, to which we turn next, would seem to be a sub-

ject in which most if not all the problems had been solved. I know of no other subject on which the concentrated efforts of such a group of great minds has been focussed. To name but some of these investigators: Flourens, Munk, Ferrier, Goltz, Luciani, Hitzig, Monakow, Bechterew and your honored guest from Holland. Yet there are a number of questions that still are unsettled.

In weighing the experimental evidence and determining the apparently great differences in some results, one point seems to have received insufficient attention, namely, that most mammals on account of the anatomic position of their eyes have complete monocular vision or at most partial binocular vision, but none of them except the monkeys have practically complete binocular vision as occurs in the human being, where each eye practically covers the same field of vision. The diametrically opposite results obtained on dogs by different investigators might readily be explained by the different type of dog used. Thus a dog with a long snout, like a hound or setter, can have no overlapping of his visual fields, while the bull-dog with the abbreviated nose undoubtedly has at least partial binocular vision. There is no doubt whatever in the case of man that each eye has representation in each visual cortex, and the most recent observations indicate though it is not absolutely proven that each macula is only represented in one cortex. It is also certain that various types of homonymous hemianopsia are produced by lesions of one optic tract after it leaves the chiasm, and similar defects may be produced at various points along this pathway (Fig. 4). Though phases of these questions are not absolutely clear the most profitable fields for investigation are the functions of the visual cortex and its location. Combining the anatomic studies of Campbell and Brodmann with the physiologic observations we know that the occipital region contains the cortical center of vision and that this area overlies Gennari's streak (Fig. 4, "A"), but what the functions of this cortex are is a debatable question (Fig. 5).

Von Bechterew believes that there are two centers, one lying on the mesial surface and one on the convexity, and that each of these centers has two separate functions, one controlling the peripheral vision and the other central vision. He furthermore believes that the center on the convexity is a higher one than that on the mesial surface and that the loss of this function leads to what the Germans have called "Seelenblindheit", the inability to interpret visual impressions. An integral part of this conception is the ability to interpret written words and musical notes. Apparently there is some further differentiation between the right and the left visual cortex, and one is forced to the conclusion that probably the left cortex in right-handed individuals plays a greater role in the interpretation of such visual impressions. In spite of these fairly well-established facts it remains difficult to differentiate

a lesion of the lateral geniculate body and the pulvinar from lesions in the optic radiation as they stream through Gennari's streak into the occipital cortex. Some observers claim that the geniculate body is more concerned with macular disturbances than the visual cortex, though the recent studies by Gordon Holmes

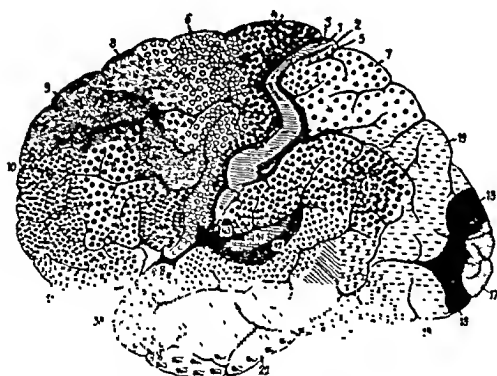
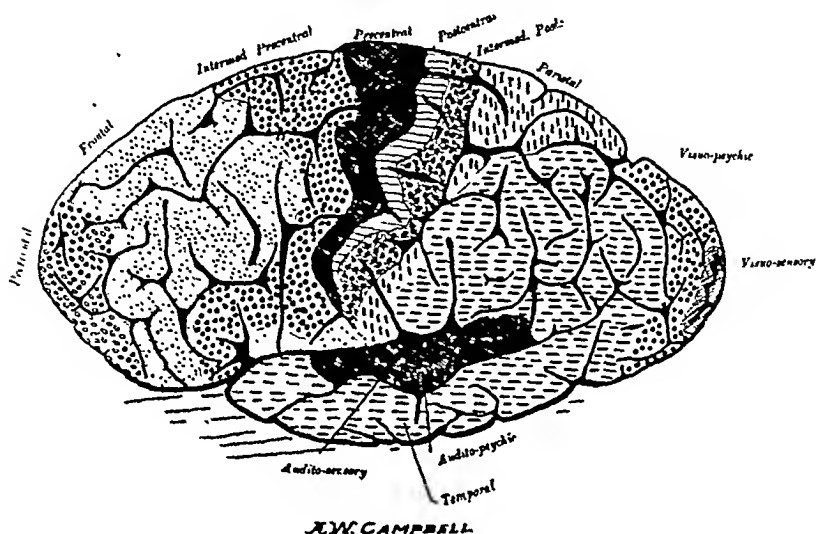


FIG. 5.—Areas of cortical function.

and by Lyster on gunshot wounds of the occipital region seem to establish the fact that the macula is represented in the cortex as is the rest of the retinal field, but each macula is represented in but one cortex—the cortex of the same side. There are those who feel that this question in regard to the macula is not yet proven. If it is so, however, the special function of the geniculate body

becomes more of a mystery than ever. We know that a lesion of this body produces a homonymous hemianopsia indistinguishable from a hemianopsia produced by lesion of the optic tract at various other points.

The interpretation and recognition of colors remains a still more uncertain question. The accepted theories of light perception all assume that the differentiation is carried out in the retina, but it seems that the cortex must exercise a further controlling influence. This is suggested by the cases in which subjective visual disturbances are noted during an attack of focal epilepsy which is due to an irritative focus in the occipital region. These rapidly passing color impressions that such patients experience are difficult to record. They are so rare that one observer rarely sees many, consequently the method of studying the phenomena is not uniform. Whether the succession of colors is always the same has as far as I know not been determined. On account of the intricacy of the problem we are offered here a most fascinating field for further investigation.

We come finally to a consideration of the sensations which are transmitted through the eighth cranial nerve. In considering these we must keep in mind that we are dealing with two separate and entirely distinct functions, those carried by the auditory portion and those by the vestibular portion.

The difference between the functions of the central and peripheral portions of the auditory mechanism is so much more clearly recognized than in the case of the other special senses that our attention is centered upon other aspects which offer greater difficulties in diagnosis.

1. The interpretation of those auditory impressions that are associated with speech and an appreciation of musical sounds.

2. The difference between disturbances of the median geniculate body, the posterior corpora quadrigemina and the auditory cortex.

The cases in which there is a partial impairment of hearing afford such opportunities for study. The first temporal convolution contains the auditory center; apparently it is divided into at least two portions, one of which controls tone and sound impressions while the other controls word impressions. Since man alone uses speech, the existence of this center in the posterior portion of the first temporal convolution can be only convincingly recognized by pathologic studies on human brains; the attempts to differentiate these centers in dogs, by supposing that howling is mere phonation, while barking, whining and snarling are akin to articulate speech, seem to me rather farfetched.

The appreciation of sounds, musical or otherwise, seems to be a bilateral cerebral function, while the *understanding* of language is confined to the left cortex in right-handed individuals.

This idea one does not at first readily accept, for speech seems



a far more universal attribute of man than does a musical sense; but a distinction must be drawn between the mere perception of sounds and the highly specialized development of the musical sense that is observed in musicians. This latter function seems to be confined to the left temporal convolution, as is speech, but the mere appreciation of sound has unquestionably bilateral representation. An individual can still hear sounds if his left auditory center is destroyed. The interpretation of auditory impressions, however, is carried out by the center in the left temporal lobe. In addition, a valuable diagnostic sign is the presence of subjective auditory phenomena. Such an individual may complain of hearing a variety of sounds or voices. These sounds may vary from time to time or always be the same. A patient with a localized tuber-



FIG. 6.—L. E. M. Surgical No. 7755. Tuberculum, 4 x 5 cm. in size, removed from auditory speech center. Present eighteen years.

culous process, a solitary tubercle (Fig. 6), said that he had for years thought he heard church bells ringing. Just why he should have had only this subjective sensation when the greater part of his auditory center was involved is difficult to explain. For diagnostic purposes it is of great importance to keep in mind that immediately underneath the cortical center of hearing lies a region—Wernicke's field—in which the fibers from the olfactory, gustatory and auditory centers lie close to one another. In consequence an irritative lesion may produce subjective sensations arising from these three centers.

The functions of the median geniculate bodies and of the posterior corpora quadrigemina are by no means clear (Fig. 4). Gerver is of the opinion that through these centers movements of the eyes

and ears are probably brought about, but the evidence is not convincing. The best opportunity for studying these regions, particularly the posterior quadrigeminal bodies, may be found in observations on early cases of pineal gland tumor. In the few cases of this sort that have been studied no minute investigations that might elucidate this point have been carried on.

The posterior quadrigeminal body also has some connections with the vestibular portion of the eighth nerve. In some investigations in my laboratory with Dr. B. Y. Alvis we have found definite anatomic connections with Deiters's nucleus, but these studies threw no light on the vestibular function of the quadrigeminal body.

The importance of differentiating the central and peripheral portions of cranial nerves is brought home to us most strikingly when we note the enormous literature that has grown up about the vestibular portion of the eighth nerve. It is, I think, fair to say that practically the entire subject of neuro-otology occupies itself with this differentiation. Interest has been centered on the functions of the nerve tracts after they leave the labyrinth.

The finer movements of coördination are conceded to be functions of the cerebellum. Bárány has located certain centers for these movements in the lateral lobes of the cerebellum. His evidence comes primarily from the study of cases of cerebellar tumors in which after operation he has frozen the overlying skin with ethyl chloride and thus affected the cerebellum. Victor Horsley and Clarke showed how inert the cerebellar cortex was. Electric currents of great strength produced no symptoms that they could recognize. I noted no disturbances when I stimulated the cerebellum on a conscious patient some years ago. This of course does not mean that such centers do not exist. The methods of examination were different. The electric current has a stimulating effect while the freezing method has a temporary paralytic effect. My own observations on one patient have the further objection that the position of a patient lying on his face during a cerebellar operation is awkward for purposes of examination. Some recent clinical studies by Gordon Holmes on gunshot wounds of the cerebellum, however, do not support Bárány's contentions that there are separate centers in the cerebellum that control movements of the extremities. Any statement from such a careful observer as Holmes carries great weight. The pass-pointing and ocular movements that are produced by stimulation of the semicircular canals are not brought about by any one center but by interaction of several centers.

Movements of the eyes may be produced by action of the ocular nuclei, an area in the frontal lobe, the lateral geniculate bodies and the anterior quadrigeminal bodies; movements of the extremities are brought about by the anterior horn cells in the cord, by

the motor cortex and probably also by the cerebellum; vestibular stimuli are transmitted from Deiters's nucleus to the roof nucleus of the cerebellum, the olivary bodies, the posterior corpora quadrigemina. Through this maze of tracts and nuclei Jones and Mills have had the great courage to attempt to explain the mechanism by which the Bárány phenomena are produced (Fig. 7). Dr. Alvis and I have worked for several years with the idea of throwing

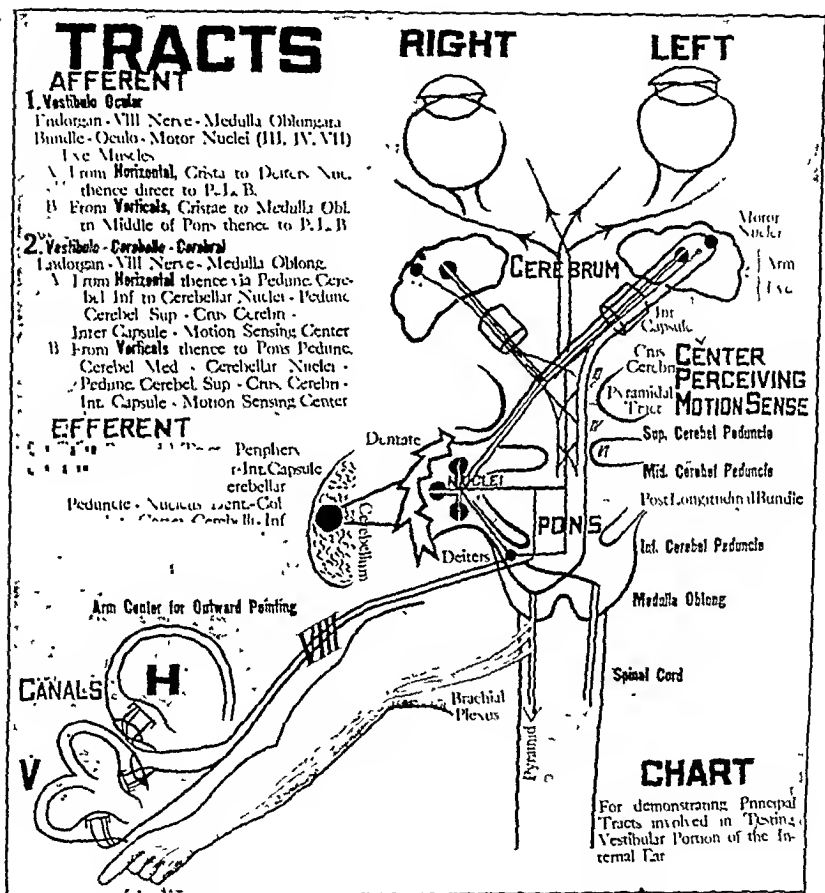


FIG. 7.—Tracts involved in testing vestibular portion of the internal ear.

some further light on the anatomy and physiology of this problem. We believe our work confirms certain points, disproves some others, but leaves other questions in a rather unsettled state. We have found a definite connection between Deiters's nucleus and the posterior corpora quadrigemina. No fibers could be demonstrated passing from Deiters's nucleus to any of the lateral lobes of the cerebellum in which the centers described by Bárány lie. Isolated lesions of Deiters's nucleus (Fig. 8) or the vestibular nerve never

produce the violent circus movements which had come to be considered as a result of von Bechterew's work diagnostic of Deiters's nucleus lesions. Such movements when they occur always are due to a lesion of the neighboring inferior or superior cerebellar peduncles.

The connections between Deiters's nucleus and the ocular nuclei as described by Fraser were not demonstrable, so that the vestibulo-ocular phenomena must be brought about by a different pathway.

We were unable to determine whether the course of the fibers from the vertical and horizontal canals followed different pathways or not on their way to the roof nucleus of the cerebellum. Again, it was not possible to demonstrate, what on theoretical

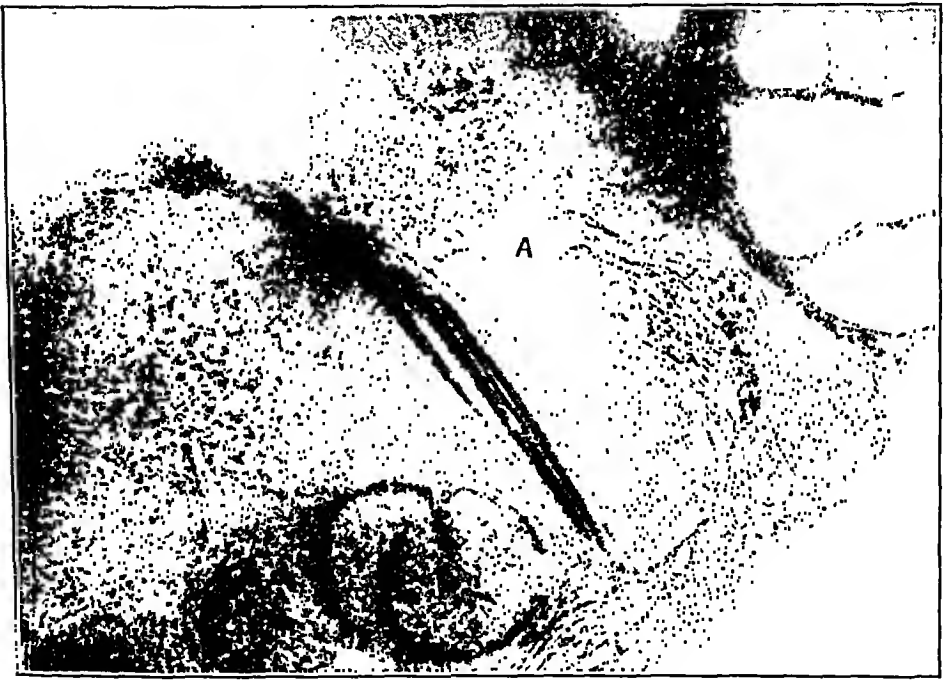


FIG. 8.—Lesion of Deiter's nucleus at A.

grounds we believe, that each semicircular canal is controlled by a separate group of cells in the Deiters's group. The most important single fact that has been established is that the tracts by which these phenomena are carried out lie immediately about the aqueduct of Sylvius and are therefore most easily affected by changes in intracranial pressure. Internal hydrocephalus is an almost invariable accompaniment of spreading processes in the posterior fossa, and the pressure of the obstructed cerebrospinal fluid frequently brings about the symptoms that have been considered evidences of local lesions. This complicating factor tends to make our knowledge of the functions of the different portions of the vestibular mechanism less certain than we have been led to believe.

If we consider for a moment what has been said this evening it must be apparent that I have passed over for the most part the facts that are well known and have tried to bring out in high relief some of the unfinished or thus far unanswered problems on the borderline of your specialties and neurology. To the earnest student these are the questions which it is most desirable to grapple with. The more difficult of solution the more worth while they are. The vast material that passes through the hands of the members of this organization contains within itself the evidence that will clear up these disputed points. To collect, correlate and subject to critical analysis all this material by uniform methods would be a fundamental and enduring service.

---

### ORTHOSTATIC ALBUMINURIA: THE STUDY OF AN UNUSUAL CASE.\*

BY WYNDHAM B. BLANTON, M.D.,

RICHMOND, VIRGINIA.

**CASE HISTORY.** Female, white, aged twenty-three years, single, school teacher.

*Chief Complaint.* Fainting.

*Family History.* Father living and well; mother died at forty-eight years of paralysis; one sister living and well; no brothers. No family history of rheumatism, gout, diabetes, cancer, tuberculosis or nephritis.

*Past History.* Patient has had the common diseases of childhood. Has not had scarlet fever, diphtheria or many sore-throats. Ten years ago she suffered with a suppuration of the glands of the neck. Eight years ago a chronically diseased appendix was removed. She has had pneumonia. Several years ago she contracted the "fever" in South America.

*Personal History.* Sleeps from 10 P.M. to 7.30 A.M. Is fond of outdoor exercise and takes more than the average quantity. Teaches school. Meals are regular; eats slowly, moderately and sparingly of meat. Drinks one cup of coffee a day. Menstruation established at twelve, regular, lasting four or five days. A moderate amount of pain precedes.

*Present Illness.* Has been given to fainting all her life. Fainted one month ago at the theater; again last night when she witnessed a harrowing picture; again today she felt that she was going to faint in school. Alarmed at the frequency of these attacks, she is seeking advice. She has recently lost some weight—from 106 to 95 pounds—and does not feel as strong as she did. She has also tingling in the hands and the feet.

\* Read before the Richmond Academy of Medicine, November 8, 1921.

*Cardiac.* No disagreeable precordial sensations; no edema of the ankles; no palpitation.

*Respiratory.* Patient has had no cough, expectoration, dyspnea, pain in the chest or night-sweats.

*Gastro-intestinal.* Her appetite is fair, bowels regular, no abdominal pain, no indigestion, no jaundice, no piles.

*Genitourinary.* No nocturia, polyuria, headaches, visual disturbances.

*Nervous System.* No abnormal symptoms. Hearing is good; no dizziness.

*Physical Examination. General Appearance.* A slender and frail young woman, with more than average alertness, who does not hold herself well and tends, when in a sitting position, to slouch.

*Constitutional Signs.* Temperature, 98.3°; pulse, 72; respirations, 18. Weight, 97 pounds. Height, 5.5. Blood-pressure, 105/70.

*Skin.* Smooth, warm, moist, no cyanosis, jaundice or edema.

*Head.* Scalp clean. Eyes: pupils dilated, round, equal, regular, react well to light and accommodation; globes move well in every direction. Nose: partial obstruction of right nostril. Ears: no discharge, no mastoid tenderness, hearing normal. Mouth: teeth good; tongue clean, straight, no tremors; pharynx and tonsils slightly congested.

*Neck.* Large scar on left side following removal of cervical gland some years ago.

*Lymph Glands.* No enlarged axillary, inguinal or epitrochlear glands. Cervical gland removed some years ago.

*Thorax.* Narrow and long, expands uniformly with respiration. Lungs: resonant throughout, no rales, no change in voice or breath sounds. Heart: normal in position and size, no murmurs, no thrills or abnormal impulses, sounds of good quality. Pulses equal, regular, and of good force.

*Abdomen.* Symmetrical, flat, muscles somewhat tense; liver, spleen and kidneys not felt; no masses, no tenderness except on right over old operative scar.

*Spine.* Examination of the back, by Dr. Wheeldon, standing, shows left shoulder higher, left scapula above the line of the right scapula, left hip prominent, with left total curvature of the spine. There is some rotation of the spine backward to the right. There is no limitation of motion; in flexion or hyperextension, but lateral motion shows a definite stiffness in the lumbar spine when bending to the right and a stiffness in the lower dorsal spine upon bending to the left. Total bending of spine to the right and left does not seem much limited. Patient's posture is bad, showing a definite rounding of the thoracic spine, with some compensatory lordosis of the lumbar spine. Pelvis is tilted forward with protrusion of abdomen to some extent. Examination, lying, shows hyper-

extension to be normal. Legs are of the same length. No limitation of motion at the hips.

*Extremities.* Negative.

*Neurological.* Cranial nerves normal, motor power normal, sensation normal; no ataxia; equilibrium normal; reflexes active.

*Fluoroscopic Examination.* Diaphragm and bony outlines of chest normal; pulmonic fields illuminate well; no increase in bronchial markings; aorta normal. Heart: normal in midline position.

*Czermac's sign* positive on both sides. Pulse slowed, 108 to 80. Patient fainted when blood was withdrawn from arm, and cardiac rate on auscultation was about forty. Eye-grounds negative.

#### Laboratory Reports:

*Blood Count.* White blood cells, 8800; polynuclears, 77 per cent; red blood cells, 4,400,000; hemoglobin, 85 per cent.

*Urine.* Amber; acid; clear; 1018; no sugar; heavy trace of albumin; no mucus, pus or blood; occasional hyaline cast; repeated thirty-five times with practically the same results.

*Urine Chlorides.* 5 gm. twenty-four hours.

*Mosenthal.* Night, 350 cc; day, 773 cc; greatest difference in specific gravity, 20.

*Wassermann.* Not done.

*Blood-sugar.* 104 mgm. per 100 cc blood.

*Blood Urea.* 1st examination, 34 mgm. per 100 cc blood; 2d examination, 12 mgm. per 100 cc blood; 3d examination, 24 mgm. per 100 cc blood.

*Phthalein.* 1st examination, first hour 50, second hour 12; 2d examination, first hour 50, second hour 25.

#### Chemical Analysis of the Protein Fraction of the Urine: Night.—

Serum albumin, 0.13 per cent. Serum globulin, 0.04 per cent. Nuclear protein, 0. Day.—Serum albumin, 0.13 per cent. Serum globulin, 0.04 per cent. Nuclear protein, 0.

Roentgen ray of spine at three levels showed no abnormality of any of the vertebrae.

#### EFFECTS OF POSTURE ON BLOOD-PRESSURE.

	Bl. P.	P. P.
Lying	130/80	50
Lying with pillow under back	130/90	40
Sitting	130/90	40
Standing	125/93	32

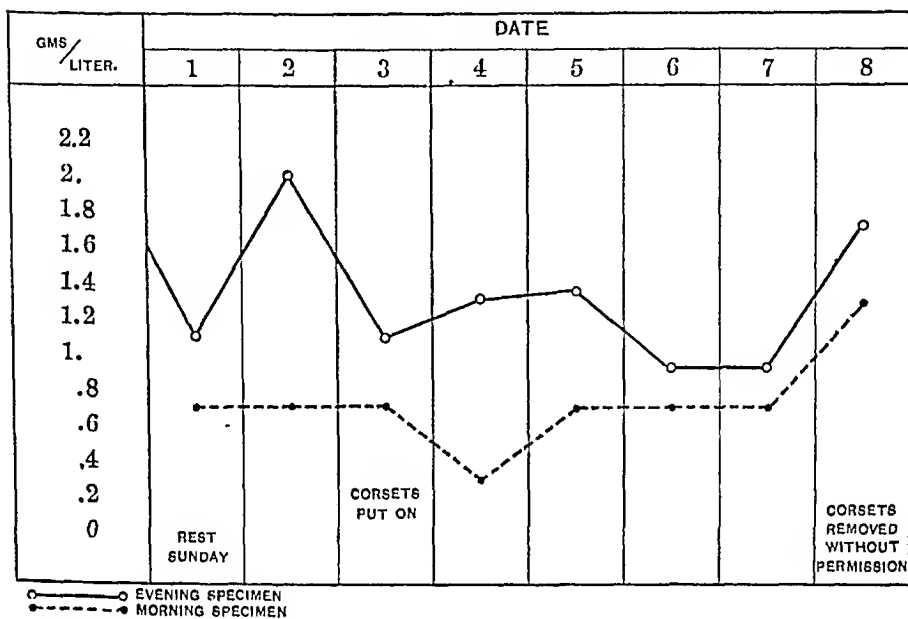
#### EFFECT OF DAY AND NIGHT ON ALBUMINURIA. DEGREE OF ALBUMINURIA.

Time.	1st day.	2d day.	3d day.
7.00 A.M.	Marked trace.	Trace.	Marked trace.
3.00 P.M.	.....	Faint trace.	Trace.
9.30 P.M.	Marked trace.	Marked trace.	Marked trace.

## EFFECT OF REST ON ALBUMINURIA\* (PATIENT KEPT IN BED FOR THREE WEEKS).

Day.	Gm. per liter of urine.
1 . . . . .	2
2 . . . . .	1
3 . . . . .	.3
4-21 . . . . .	.3-.5

## EFFECT ON ALBUMINURIA OF WEARING LIGHT PLASTER JACKET ONE WEEK.



*Diagnosis.* 1. Syncope of vagal origin. 2. Albuminuria, orthostatic.

*Discussion.* The escape of coagulable proteins from the blood and their appearance in the urine are generally conceded, though not proved, to be due to an alteration in the glomerular tuft, resulting in the permeability of this structure for substances commonly called albumin. The occurrence of a coagulable protein in the urine (putting aside pus, blood, spermatorrhea, etc.) is common in disease and occasional in health. The acute and chronic diseases of the kidney characterized by albuminuria are well known. During what we consider as good health albumin not infrequently makes its appearance in the urine. Frequently albumin may appear in the urine after severe exercise, cold baths, mental strain or the ingestion of raw protein, such as egg albumen. Albuminuria of longer duration occurs in the newborn and in pregnancy (about 50 per cent). So-called essential albuminuria (Sahl<sup>3</sup>) may last for years and includes the albuminuria of adolescence (von Leube) and orthostatic albuminuria.

In describing the condition of orthostatic albuminuria various synonyms have been employed by different authors. It has been called also lordotic, intermittent, postural, cyclic and physiologic.

\* Two months after getting out of bed albumin had again mounted to 2 gm



To fulfil the diagnostic postulates generally given of this condition the patient must repeatedly show albuminuria in the erect position which disappears in recumbency. A few hyaline casts may or may not be present. Other evidence of nephritis must be excluded.

Roger I. Lee<sup>1</sup> in a discussion of albuminuria in healthy young men makes a threefold classification: (1) Those who show albumin only during the day—strictly postural albuminuria and including by far the largest number; (2) those who show small amounts of albumin occasionally; (3) those who show albumin in all specimens both day and night. It is our belief that this classification is correct and, further, that so-called postural albuminuria is really a subhead of the albuminuria of adolescence. These types represent different grades of the same disturbance. However, as in our case, the fact that with rest even the severest form tends to great reduction in the amount of albumin shows that the postural factor plays an important part here as elsewhere.

The explanation of this striking condition has been variously set forth. Foremost is the postural theory, which makes lumbar lordosis the mechanical factor interfering with the return renal circulation, which in turn is said to produce congestion of the kidney with sufficient glomerular stasis to allow of a leak of albumin. Since Jehle<sup>3</sup> showed that lordosis was an almost constant finding in this type of albuminuria, that lying down would rid patients of their albumin, and that albumin-free and otherwise normal children could be made to show albumin by artificially produced lordosis, this explanation has been widely accepted. Others supporting this theory are L. Jeanneret,<sup>4</sup> G. Pechowitsch,<sup>5</sup> K. Dietl,<sup>6</sup> G. Turrettini,<sup>7</sup> L. Piesen,<sup>8</sup> A. Lury,<sup>9</sup> R. Fischl,<sup>10</sup> H. Nothmann,<sup>11</sup> J. M. Hamelberg,<sup>12</sup> Roger I. Lee,<sup>2</sup> M. H. Bass,<sup>13</sup> L. F. Barber and F. J. Smith.<sup>14</sup>

Erlanger and Hooker<sup>15</sup> advanced another theory—that the diminished pulse-pressure occurring in these patients in passing from the reclining to the erect posture is responsible for their condition. They maintain that the normal difference in maximal and minimal pressure, or pulse-pressure, acts as a pounding force in the kidney, and to keep up the normal renal circulation, which is accompanied by no albuminuria, this range of variation in blood-pressure is necessary. The diminished pulse-pressure in the erect position, said to be characteristic of orthostatic albuminuria, therefore permits of renal congestion, and hence of albuminuria.

K. Dietl<sup>6</sup> assumes that these abnormal blood-pressure changes are based upon vasomotor instability. He has, however, given a name and not an explanation of this phenomenon. R. von Stejskal<sup>16</sup> holds to a similar explanation. Mason and Erickson<sup>17</sup> also champion this theory in a recent article illustrating their argument from five cases. Some authors have considered a floating kidney responsible for the urinary findings. The idea of Tissier<sup>18</sup> that this condition is due to a congenital histologic anomaly resulting in an increase of glomerular permeability has nothing in fact to substantiate it.

In the final analysis it appears that the best evidence goes to show

that the most probable explanation of postural albuminuria lies in lordosis, with or without vasomotor stigmata, in the constitutionally predisposed.

We are fortunately not without valuable statistical studies relating to the incidence of albuminuria in healthy adolescence, numerous authors having investigated exhaustively this phase of the subject.

Lee<sup>2</sup> found that 5 per cent of 5000 so-called healthy young men of college age showed albumin in the urine. Only 0.1 per cent of these had nephritis. Maclean<sup>19</sup> among British soldiers during training found 5 per cent of 50,000 examined with albuminuria. Of these, 3 per cent had only very slight albuminuria. Reber and Lauener,<sup>20</sup> in Switzerland, showed that of a battalion of 528 healthy soldiers examined, 10 per cent gave a reaction in the urine for albumin. Bugge<sup>21</sup> claims to have found 15 per cent of albuminuria among 1076 school children examined. Gotzky<sup>22</sup> in children also gives high percentages—among 346 examined, 14 per cent were the subjects of albuminuria. Hamelberg<sup>12</sup> also studied school children. Among 401 boys he found 8 per cent with albuminuria; among 311 girls, 22 per cent. Albuminuria in adolescence, therefore, is encountered with surprising frequency.

One in a thousand of Lee's<sup>2</sup> cases had albuminuria with evidence of kidney disease. Of Maclean's<sup>19</sup> 50,000 soldiers examined during training 132 subsequently entered the hospital with war nephritis, but only 17 per cent of these had shown albuminuria during their training period. Various authors have studied the functional capacity of the kidney in postural albuminuria. Their findings almost uniformly show the kidney free from the changes characteristic of nephritis.

Mason and Erickson<sup>17</sup> did "phthaleins" on 5 cases and Barker and Smith<sup>14</sup> report results of 6 patients similarly tested. There were no abnormal findings. Lee<sup>2</sup> found normal functional tests in his cases which were not nephritic. In 662 men, 12.8 per cent had a labile systolic blood-pressure of 140 or more due, it was thought, to nervousness. Among this group, however, he discovered albuminuria twice as often as among others with normal blood-pressure. Jehle<sup>3</sup> pointed out that albuminuric patients may show oliguria with low salt output while up and about, and that these abnormal findings disappear when these same patients are put to bed. Mason and Erickson<sup>17</sup> state that casts are usually absent. Lee<sup>2</sup> found them in 15 per cent of his cases. Maclean<sup>19</sup> claims, on the other hand, to have found casts in only 1.8 per cent of the 50,000 men he examined.

Sahli<sup>1</sup> quotes von Leube as stating that the age incidence of orthostatic albuminuria is between the fourteenth and eighteenth year. Mason and Erickson<sup>17</sup> quote Lommel as finding this condition chiefly between fifteen and twenty-one, while they themselves give sixteen to twenty-two as the period when it is most liable to appear. The great mass of the literature on the subject is given over to the study of this condition in school children. One of Mason and Erickson's<sup>17</sup> cases, however, was a man forty-three years old.

Barker and Smith<sup>14</sup> cite cases twenty-four and twenty-five years of age respectively. It may be stated then that while the condition occurs with fair frequency in adolescence it is distinctly uncommon after this age. The sexes seem to be equally affected.

So definite is the relation of these urinary findings to certain physical characteristics that most authors describe an orthostatic type of individual. These patients present physical characteristics of which lordosis and other spinal curvatures are but a single manifestation in a complex constitutional weakness or defect. They are nervous, anemic, lean and poorly nourished individuals, subject to vasomotor instability, ptoses and postural faults.

Most writers agree in assuming an optimistic outlook with reference to improvement, believing that the albuminuria itself is not a serious occurrence, related as it is to no known structural disease of the kidney. Treatment offers hopeful results. Lee<sup>2</sup> as well as others cite striking improvement with the vertebral brace, abdominal supports and lumbar muscle exercises.

**SUMMARY.** A case of persistent albuminuria in a young woman has been described. The history, physical examination and functional tests of the kidneys failed to show evidence of nephritis. Albumin persisted at the expiration of three weeks in bed, making it difficult at first glance to reconcile this case with the usual description of orthostatic albuminuria. However, the marked reduction of albuminuria (from 2 to 0.3 gm.) with rest and support of the back makes the condition clearly of the same general category of the postural or orthostatic albuminuria, though probably of a more severe grade than usually encountered. The evidence of a vasomotor disturbance in this patient has been brought out, and this additional factor may account for the persistence of albuminuria with rest.

#### BIBLIOGRAPHY.

1. Sahli, H.: *Diagnostic Methods* (Potter), 1911.
2. Lee, Roger I.: *Med. Clin. North America*, 1920, 3, 1059.
3. Jehle, L.: *München. med. Wehnschr.*, 1908, 55, 12.
4. Jeanneret, L.: *Arch. de méd. des enfants*, Paris, 18, 461.
5. Pechowitsch, G.: *Deutsch. med. Wehnschr.*, Berlin, 36, 1985.
6. Dietl, K.: *Wien. klin. Wehnschr.*, Vienna, 26, 241.
7. Turrettini, G.: *Revue de méd.*, 29, 673.
8. Piesen, L.: *Wien. klin. Wehnschr.*, 24, 1.
9. Lury, A.: *Jahrbuch. f. Kinderheilk.*, Berlin, 72, 661.
10. Fiehl, R.: *Arch. f. Kinderheilk.*, 52, 241.
11. Nothmann, H.: *Arch. f. Kinderheilk.*, Stuttgart, 49, 161.
12. Hamelberg, J. M.: *Nederlandsch. Tydschrift voor geneeskunde*, Amsterdam, 1918, No. 10, 1.
13. Bass, M. H.: *Med. Clin. North America*, March, 1921.
14. Barker, L. F., and Smith, J. F.: *AM. JOUR. MED. SC.*, 1916, 151, 44.
15. Erlanger and Hooker: *Johns Hopkins Report*, 1904, 12, 145.
16. R. V. Steuskal: *Wien. klin. Wehnschr.*, 21, 453.
17. Mason, E. H., and Erickson, R. J.: *AM. JOUR. MED. SC.*, 1915, 156, 643.
18. Tissier: *Revue de méd.*, 1905, 25, 233.
19. Maclean, H.: *British Med. Jour.*, 1919, 1, 94.
20. Reber, M., and Lauener, P.: *Correspondenz-Blatt f. Schweizer Aerzte*, Basel, 45, 897.
21. Bugge, J.: *Norsk-Magazin for Laegevidenskaben*, Christiania, 74, 1601.
22. Götzky, F.: *Jahrbuch f. Kinderheilk.*, Berlin, 71, 379.

## REVIEWS.

---

LESSONS IN PATHOLOGICAL HISTOLOGY. By GUSTAVE ROUSSY, Professeur Agrégé and IVAN BERTRAND, Chef de Laboratoire des Maladies Nerveuses, Université de Paris. Translated from the second French edition by JOSEPH MCFARLAND, Professor of Pathology and Bacteriology in the Medical Department of the University of Pennsylvania. Pp. 268; 124 engravings. Philadelphia and New York: Lea & Febiger, 1922.

For a work of its size, this small book contains a surprisingly large fund of information, clearly exposed in convenient form. Opposite each page of text is the corresponding illustration with very satisfactory descriptions. In most of the illustrations, however, the magnification is so small, that while details would doubtless be recognizable to one already familiar with the subject, it is questionable whether they would be of equal value to the beginner, for whom such a book is designed. Figs. 2, 46 and 64 are notable exceptions. Although the subject-matter is based upon the course given in the University of Paris, it does not, according to the preface, aim at a complete presentation, but rather to teach the student the correct method. As an accompaniment then to a more complete book, it should prove to be of value. K.

HAYFEVER AND ASTHMA: CARE, PREVENTION AND TREATMENT. By WILLIAM SCHEPPEGRELL, A.M., M.D., President, American Hayfever Prevention Association; Chief of Hayfever Clinic, Charity Hospital, New Orleans. Pp. 274; 108 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

THIS book is an excellent contribution to the literature. From the standpoint of the etiology of hayfever and (as the title should more specifically read) hay asthma, it is the most complete statement of the subject available, representing as it does the result of years of work by the author and his associates in the American Hayfever Prevention Association. There is a survey of the hayfever producing plants, their distribution and period of pollination throughout the United States, with detailed descriptions and

illustrations of some of the most important. Over two hundred plants, including many that have been wrongly suspected of causing hayfever, have been investigated. There are tabulated for each state the local causes of hayfever, and, when they exist, "hayfever resorts"—localities in which the offending plants are scarce or absent. The botanic characteristics that make a plant a potential hayfever cause, namely, wind pollination—a pollen that is produced in large quantities, and whose grains are sufficiently small to permit of wide wind convection—are well demonstrated and emphasized. It is pointed out that hayfever is, in a measure, preventable and there are discussed educational and legislative measures for weed control, based on the gratifying results obtained under the author's guidance in New Orleans. The chapter on treatment is adequate. It is to be regretted, however, that the author has not gone into a little more detail as to treatment and results, perhaps with illustrative case histories. A disease that afflicts 1 per cent of the population demands the attention of every practitioner. The author's well written and profusely illustrated book can be highly recommended.

R. A. K.

---

THE THYROID GLAND. By GEORGE W. CRILE, M.D., and Associates at the Cleveland Clinic, Ohio. Pp. 228; 106 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THE purpose of this volume as stated in its introduction is to present the present theoretic and practical viewpoints of the author and his associates on the subject of the thyroid gland. It is admittedly but an ephemeral publication, and does not purport to be a textbook or a monograph and will be constantly subject to revision and possibly reversal of opinion. The book is composed of twenty-two separate articles, eight of which are at least in part written by the senior author; the others are by his associates in the Clinic staff. Several are highly theoretical and in their present brief form unconvincing. The rest are extremely practical and detailed, and their worth may be estimated from the fact that they represent the actual working methods of one of the most efficient surgical clinics in the world. Special mention must be made of the articles on the preoperative and on the postoperative treatment of the exophthalmic goiter patient. Throughout the book one finds a tendency to lay more stress on the so-called Goetsch test than is the rule elsewhere, and conversely less emphasis is placed on the estimation of basal metabolism. There is something in the book of value for every physician who is concerned with thyroid disease and there is much of value for every surgeon. This value is to be found in the practical rather than in the theoretical sections of the book.

O. H. P. P.

DISEASES OF THE EYE. By MAY, Visiting Surgeon, Eye Service, Bellevue Hospital; Attending Ophthalmic Surgeon, Mt. Sinai Hospital, New York. Tenth Edition. Pp. 426; 377 illustrations. New York: William Wood & Company, 1922.

THIS manual describes the more common diseases of the eye at sufficient length to give one a clear idea of the etiology, symptoms and treatment. Where the pathology is important it is briefly discussed. The contents are arranged systematically, starting with a description of the different methods of examination.

The illustrations are excellent and include twenty-two plates, with seventy-one colored figures.

The chapter on "Disturbances of Motility of the Eye" is especially helpful because of its diagrams.

This book could be recommended as a manual, but should not be substituted for a text-book.

H. W. S.

---

SURGICAL CLINICS OF NORTH AMERICA, VOL. II, Nos. 2, 3, 4. Pp. 820; 453 illustrations. Philadelphia: W. B. Saunders Company, 1922.

THESE three numbers, from San Francisco, Chicago and Boston, give the reader some most interesting and valuable information. The contributors are those standing among the highest in the profession and it seems as though these same writers have endeavored to put forth their utmost to present valuable articles. The contributions cover well the entire field of surgery, with the exceptions of the restricted specialties. Excellent articles are given on bone, joint, intestinal, kidney, tendon, hand and other subjects from both the surgical and pathologic standpoints.

I wish again to state here that the character of the *Clinics'* products is daily and rapidly approaching the really valuable clinical presentation, where padding with non-essential historical and clinical data is taboo, and only the essentials for diagnosis and treatment are noted.

E.

---

MEMORIAS DO INSTITUTE OSWALDO CRUZ. Volume XIII, 1921.

This volume contains two valuable articles. One is entitled "Contribution to the Study of the Helminthologie Fauna of Brazil," by DR. LAURO TRAVASSO. The monograph deals especially with the morphology of the family Trichostrongylidæ, and comprises 140 pages fully illustrated with 56 plates and figures.

The other article is entitled "Observations upon Two Genera,

Urogonimus and a New Form of Leucochloridium, in a New Host," by DR. ADOLPH LUTZ. The writer believes this Leucochloridium to be a new species found in Brazil, and different from the Leucochloridium described by Monticelli in Europe and that described by Magath in America.

---

R.

THE INTESTINAL PROTOZOA OF MAN. By CLIFFORD DOBELL, M.A., F.R.S., National Institute for Medical Research, London; and F. W. O'CONNOR, M.R.C.S., L.R.C.P., D.T.M. and H., London School of Tropical Medicine. New York: William Wood & Company, 1921.

As the title indicates, this book represents the result of the observations and studies by the authors on the intestinal protozoan parasites of man as they are found in England, in which is included a review of the work of other investigators upon these parasites. The book is divided into nine chapters and consists of 221 pages and 8 plates.

A general introduction to the subkingdom protozoa and its four phyla, and descriptions of the known amebas (four genera and five species), flagellates (five genera and five species), coccidia (two genera and four species) and ciliates (two genera and three species) are given in separate chapters, which also include the pathology and symptomatology of the respective infections.

The outstanding feature of this book is the fact that in its preparation are combined the experience and efforts of a zoölogist and a medical man, as is clearly manifested in the character of the zoölogical and medical consideration of the subject discussed. The diagnosis and treatment of intestinal protozoal infections are discussed, in which the laboratory man and the clinician will find many helpful and valuable suggestions. The last chapter contains a very useful and practical discussion of the Coprozoic protozoa of man.

The authors may be criticized for their rather radical attitude in some features of the book, such as the description of the so-called *iodin cysts* in amebas (Dobell), which probably need further confirmation, as to the omission in the book of the description of *Entameba paradysenteriae* (Chatterjee); of *Entameba macrohyalina* (Tobaldi); the statement that the cyst of *Trichomonas hominis* and the cultivation of this parasite *in vitro* has not been satisfactorily demonstrated; the doubt as to the existence of so many structures in the small cyst of *Chilomastix mesnili* (Kofoid and Swezy) and their view regarding the nuclear division. It should be borne in mind that these statements express the authors' personal experience. To be sure, they reflect a rather wholesome conservative attitude which is commendable in view of the tendency

to premature conclusions, often encountered, regarding the discovery of new facts or new species among protozoa.

The book, as a whole, is fairly complete, logical in its arrangement and precise in its description, and written in an attractive style. This work may be considered a valuable contribution to the study of the intestinal protozoa parasites of man, and will be found of great assistance to laboratory workers and physicians in the diagnosis and treatment of these infections. R.

# STUDIES ON THE HISTORY AND METHOD OF SCIENCE, VOL. II.

Edited by CHARLES SINGER. Pp. 559; 55 plates and 80 illustrations. Oxford: Clarendon Press, 1921.

As the title suggests, this is a collection of papers by various authors, containing reviews and discussions of the earliest application of scientific methods in the growth of medicine. There is a wealth of detail and a pleasing discussion in each chapter. It is impossible to enumerate in a brief space the wonderfully interesting and scientific data compiled here. The subject-matter covers chemistry, mathematics, physics, metaphysics, philosophy, botany paleobotany, religion and language.

The first and tenth chapters are written by Charles Singer, bearing the titles, "Greek Biology and its Relation to the Rise of Modern Biology" and "Steps Leading to the Invention of the First Optical Apparatus." The former is intensely interesting in a comparative analysis of the early Greek methods and the present-day investigations.

J. L. E. Dreyer contributes a pleasing history of "Mediæval Astronomy." The fourth chapter, written by Robert Steele, has an account of "Roger Bacon and the State of Science in the Thirteenth Century." One obtains a clear appreciation of the difficulties attending scientific pursuits at that time and marvels at the persistence of these pioneers in pursuing their investigations in spite of almost insurmountable opposition.

H. Hopstock portrays, from a translation from the Norwegian by E. A. Fleming, a study of "Leonardo as Anatomist." It is exceedingly well written and emphasizes the versatility and love of sciences of one of the greatest men of the ages. In the fifth chapter E. T. Withington discusses "Aselepiadæ and the Priests of Asclepius." The "Scientific Works of Galileo (1564-1642), with Some Account of His Life and Trial" is a thorough and clear review of Favaro's edition by J. J. Fahie. The thoroughness of Favaro's work is better understood when we learn that he spent forty-four years in his study of the life and works of Galileo.



The "History of Anatomical Injections" in the seventh chapter, by J. H. Cole, should be of profound interest to every student of medicine. The eighth chapter is written by F. S. Marvin on "Science and the Unity of Mankind" and is a masterly production. F. S. Conybeare appears in the succeeding chapter with an article entitled "Four Armenian Traacts on the Strueture of the Human Body," which is of considerable historic value. The eleventh chapter is written by F. C. Schiller on "Hypothesis." J. M. Jenkinson has written about "Science and Metaphysics," while the thirteenth chapter contains a "Sketch of the History of Paleobotany," by E. A. Newell Arber.

J. M. Child has given a delightful criticism of "Archimedes's Principle of the Balance." Arthur Platt contributes the last and fifteenth chapter, with the title, "Aristotle on the Heart." There is in addition an appendix and index covering twenty-six pages.

The book is excellently written, is clear in style and illustrated generously with plates and figures, which are unsurpassed. It is only necessary for one to read the entire list of contributions in order to obtain an idea of the scope of the work. One readily realizes after reading this book what a debt medicine owes to the ancient Greeks and the prominent scientific men through the Middle Ages, for the great contributions which they have made and which are used today as the foundations for a great many of our classifications, ideas and methods in scientific work. It seems that the Greeks were prone to the same errors as modern writers, in that they gave results of experimental work without instructing the reader as to the means by which they came to their conclusions.

Nothing but praise can be given in the way of criticism on this book, and every medical man will find in it facts concerning the origin and development of scientific principles, gathered together in one volume, which it would take him a great amount of time to find or read were he to search for the same independently. P.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**Bismuth in the Treatment of Syphilis.** — CLEMENT SIMON and J. BRALEZ (*Bull. méd.*, 1922, 36, 523) review the recent literature regarding the treatment of experimental and human syphilis with various salts of bismuth, the most important of which is sodium and potassium tartro-bismuthate. The first Congress of Dermatology and Syphilis, which just took place at Paris, devoted a whole session to reports of investigations with these drugs. The authors report their own experience in the treatment of 113 cases of syphilis with the insoluble bismuth salts. They employed four different preparations of sodium and potassium tartro-bismuthate. The route of the administration was intramuscular, the drug being given in oily suspension. The dosage was 20 eg., each injection being given twice a week, a course of treatment consisting of from 6 to 12 injections. The authors find that the reactions from the use of this drug are in general those described by previous investigators. The most important reaction is stomatitis, which occurred in about 12 per cent of all cases treated. In a somewhat higher proportion of cases, however, there appears also a bluish line on the borders of the teeth and large bluish spots on the internal surface of the cheeks, this pigmentation being similar to that observed in chronic lead poisoning. In practically all instances the stomatitis was mild and cleared up promptly on the cessation of bismuth treatment. An additional 12 per cent of patients developed reactions of other types during the course of treatment, these reactions being for the most part cramps, malaise, nausea, headache, and a single reaction simulating nitritoid crisis after arsphenamine. In general, reactions of all types

were mild and did not interfere to any great extent with the treatment. So far as the therapeutic results are concerned, treponemes disappeared within two to fourteen days from chancres and from the mucous lesions of secondary syphilis. Chancres were healed in the average of fourteen days after a total of 4 injections, whereas the lesions of secondary syphilis healed in an average of twenty-two days after 6 injections. A number of cases of latent Wassermann positive syphilis were treated, but the authors conclude that too little time has elapsed to permit any evaluation of the serologic results. Their impression is that bismuth acts less rapidly than arsphenamine on the Wassermann reaction. They treated 3 cases of cerebro-syphilis and 7 of tabes dorsalis. In several of these there was notable improvement in clinical symptoms, but no change occurred in the cerebrospinal fluid findings. They conclude that the salts of bismuth may prove to be of great value in the treatment of syphilis, particularly in those cases, unfortunately too common, which are intolerant of arsphenamine and mercury.

---

**Absorption of Digitalis in Man.**—CARY EGGLESTON and JOHN WYCKOFF (*Arch. Int. Med.*, 1922, 30, 133) report upon the rate of absorption of especially purified tincture of digitalis and of various official tinctures of the same drug. With the exception of certain details, the results agree with previous work of Eggleston and others upon the therapeutic dosage of digitalis in proportion to body weight. The conclusions are not in accord with a report of Wedd who found that: "No constant relation between the amount of digitalis that could be given and the age or body weight of the patient or the condition of the myocardium could be discovered." Eggleston and Wyckoff used in most of their work a chloroform soluble extract of digitalis in alcohol, which they call a "purified tincture." With this preparation the greatest total range of variation in effective dosage was between 23 per cent below and 21 per cent above the average dosage. In this respect the purified tincture was more uniform than "official" tinctures. The absorption of the purified tincture was two to three times as rapid as that of galenic tinctures. It was found that tincture of digitalis shows definite evidences of action on the heart in from two to four hours after oral administration to man. Evidence is offered to show that digitalis causes nausea or vomiting in man by reflexes arising in the heart as a result of the intoxication. The authors advocate doses of digitalis more conservative than those formerly suggested. It is now believed that 0.1 cat unit of the drug per pound of body weight of the patient represents fairly well the average full therapeutic dose.

---

**Diastolic Activity of the Heart.**—SIEWERT, A. K. (*Ztschr. f. d. Ges. Exp. Med.* 1922, 28, Hefte 5 und 6) divides diastole into two distinct parts and produces experimental evidence to show that there is an active phase of diastole late in the long period of the heart's cycle. Observations were made upon the interventricular pressure throughout systole and diastole by exposing an animal's heart and inserting a recording manometer directly into the ventricle. It was found that under ordinary conditions there is comparatively little negative pressure within the ventricle, whereas this negativity may be increased by 200 or more per cent by cardiac stimulation, for example, by injecting

strophanthin into the pericardium. Sicwert considers that the relative activity of diastole at any particular moment can be measured by the degree of negative pressure that obtains within the ventricle. The point at which the greatest negativity begins he calls D, and electrocardiographic studies have shown that D corresponds to the beginning of auricular systole. He, therefore, concludes that the heart participates actively in its own filling during a short phase at the end of ventricular diastole. Such a theory of cardiac mechanism may have considerable bearing upon the mode of production of presystolic gallop rhythm and presystolic murmurs.

---

## SURGERY

---

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

---

**Epithelioma of the Genitourinary Organs.**—BRODERS (*Ann. Surg.* 1922, 75, 574) says that epithelioma of the genitourinary organs occurred more often in females than in males; the proportion was about three to one. Approximately 12 per cent of the author's series had a family history of malignancy. The average duration of the lesion in all of the patients was 1.35 years. Over 90 per cent of the patients were operated upon. Twenty-three per cent of all the patients are alive with good results while 70.5 per cent obtained poor results, living for an average of 1.34 years. Ten per cent of patients with large cervical lesions obtained good results, while 33 per cent of those with medium-sized lesions had good results. One hundred per cent of patients with small lesions obtained good results. In all, 20 per cent or one in five obtained good results, with cervical lesions. Patients with lesions of labia show relatively the same percentages. Forty-eight per cent or nearly one-half of the patients with lesions of the bladder obtained good results, while 41 per cent of patients with lesions of the penis obtained good results.

---

**Hernia of the Bladder.**—BAKER (*Ann. Surg.*, 1922, 75, 615) says that the majority of bladder hernias are in fact false hernias as they either have no peritoneal sac at all or the bladder is found alongside the hernial sac instead of within the sac. According, therefore, to the manner in which the peritoneum is involved in these bladder hernias the classification is given as extraperitoneal, paraperitoneal and intraperitoneal (or true bladder hernia). The possibility of bladder involvement should always be suspected and due caution observed in all large inguinal hernias, more especially those of advanced life and in those manifesting prostatic hypertrophy or other signs of crippled bladder

function; in all direct inguinal hernias regardless of size or age; in all operations for recurrence of hernia, for recurrences are notoriously of the direct type and adhesions about the neck of the sac from the former operation result in a possible pull on and displacement of the bladder. In all hernias presenting an undue amount of fatty tissue closely associated with the sac, at or near the fovea inguinalis medialis, the possibility of injury to the bladder is increased and this danger signal should never go unheeded.

---

**The Cause of Death in High Intestinal Obstruction.**—ELLIS (*Ann. Surg.*, 1922, 75, 429) says that in cases of high obstruction a poison can be isolated by precipitation with alcohol, extraction with boiling water and reprecipitation with the aid of magnesium sulphate. It is not possible to obtain such a poison with this method from the intestinal content of a normal dog prepared immediately after removal. A poison which, when judged by the means at the author's disposal, is identical, can be obtained from conditions other than actual obstruction, such as the intravenous injection of the obstruction toxin into normal animals, the removal of the adrenals, portal obstruction and in experimental acute non-bacterial peritonitis. This poison is undoubtedly elaborated in the cells of the greater part of the mucosa of the small intestine but chiefly in those of the duodenum. It is manifestly excreted partly into the lumen of the intestine, but the larger part passes into the lymph stream. The clinical similarities between acute pancreatitis and high obstruction are due either to a close relationship between the toxins involved or possibly to the fact that acute pancreatitis actually produces conditions in the intestinal mucosa favorable to the production of the same toxin as is found in cases of high obstruction. Since erepsin fails to exert any action upon the toxin and since the toxin shows no lymphagocic action whatever, it seems necessary to conclude that the toxin is neither a proteose nor a heteroproteose. The finding of the toxin in the intestinal content after the removal of the adrenals suggests that clinically adrenalin should be added to the saline infusion.

---

**Non-tuberculous Kidney Infections.**—SULLIVAN (*Ann. Surg.*, 1922, 75, 473) says that the kidney is the eliminating organ for circulating bacteria and in the course of this elimination may itself be damaged in a variety of ways. Hematogenous infection may be restricted not only to a single kidney but even to a circumscribed portion of the organ. The source of the infection may not only be a general disease but a distant and apparently insignificant focus may be responsible. Metastatic hematogenous infection of the kidney, perinephritic or paranephritic abscess, is not always easily recognized and may be confused with intraabdominal infections. A sudden attack of pain in the kidney region associated with fever in a patient known to have a suppurative process elsewhere in the body should excite suspicion of metastatic kidney infection. Cystoscopy and pyelography are valuable aids, especially when urinary changes are incomplete or the symptoms are referred to the healthy side. The treatment of perinephritic or paranephritic abscess is early drainage. When the suppuration involves the kidney parenchyma or where the process is an acute fulminating one, nephrectomy is indicated.

**Tuberculous Empyema.**—HEDBLÖM (*Surg., Gynec. and Obst.*, 1922, 34, 445) says that primary or idiopathic pleurisy with effusion in a large proportion of cases is probably tuberculous in nature. A past history of pleurisy with effusion is common in cases of tuberculous empyema. In many cases the effusion is serous at the onset. Tuberculous pleurisy may be primary or it may be secondary to a pulmonary, peritoneal or other tuberculous lesion. The onset of a tuberculous effusion may be insidious or it may be sudden and associated with an acute and severe constitutional reaction. A mixed pleural infection due to the perforation of a tuberculous cavitation often runs an acute and rapidly fatal course. Diagnosis of tuberculous empyema is made by demonstration of the bacilli in the exudate, by animal inoculation or by examination of the sectioned pleura. A sterile effusion is probably tuberculous. An infected effusion may be tuberculous. Empyema following primary idiopathic pleurisy with effusion or empyema of insidious onset, especially in the presence of a pulmonary or other tuberculous condition, is probably tuberculous. Empyema may be tuberculous in spite of persistently negative findings over a long period of time. In a closed pleural cavity a sterile effusion, whether serous or purulent, should not be treated by open drainage except in the presence of an impending perforation of the chest wall. Repeated aspiration of only part of the fluid present is indicated in cases of serous effusion, producing definite dyspnea on exertion or symptoms of circulatory embarrassment. The replacing of aspirated fluid by nitrogen or filtered air may be indicated in cases in which there are symptoms of active phthisis referable to the same side as the effusion. A sterile purulent effusion should be treated as though it were serous if the lung expands when fluid is withdrawn. If the lung is fixed in a collapsed condition or if the effusion persistently recurs an extrapleural plastic operation is indicated. Effusion in a closed cavity showing a mixed infection should be treated by the closed method with antiseptic solution irrigation or by open drainage; the open drainage is indicated especially in cases of severe infection associated with extensive pulmonary tuberculosis, making irrigation hazardous. Tuberculous empyema with a large bronchial fistula should be drained by the open method. A plastic operation involving closure of a bronchus offers the only prospect of a cure in case of an associated large bronchial fistula. An extrapleural rib resection is indicated for the collapse of closed sterile cavities. Cases of long standing associated with greatly thickened pleura require an extensive resection of the entire chest wall after the method of Schede.

---

**Human Actinomycosis.**—MATTSON (*Surg., Gynec. and Obst.*, 1922, 34, 482) says that there is but one true species of microorganism capable of producing actinomycosis in man and lower animals, and this is the one indicated by Wolff and Isreal and later more fully described by Wright. There is no convincing clinical and biological evidence that this microorganism has its source outside of the human body; as a saprophyte in old sod soil from which it gains access to grains and grasses and through this medium or intermediary host, so to speak, it becomes capable of infecting man and lower animals. In order for infection to take place two things are necessary: first, an abrasion of the tissues; second, the

fungus must in some way be brought directly in contact with this abrasion. Human actinomyces is not a rare disease but a disease which is often overlooked or incorrectly diagnosed. Every inflammatory swelling of chronic or subacute nature with persistent and recurring sinus formation should be carefully investigated for this disease. The disease should always be kept in mind in every case of a typical pulmonary tuberculosis and should be looked for in cases suffering with chronic purulent bronchitis. Early treatment of superficial lesions are highly successful. Internal infections are extremely fatal and hopeless.

---

## PEDIATRICS

---

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

---

**The Relation of Nutrition and Tooth Development and Tooth Preservation.**—McCOLLUM, SIMONDS, KINNEY and GRIEVES (*Bull. Johns Hopkins Hosp.*, 1922, 33, 202) studied this problem in rats. They found that the internal structure of the skeleton of the rat could be changed at will by varying the ration which the animals received. Bone is an extremely labile tissue and is readily influenced by nutritional environment. Some of the faulty diets which were studied produced rickets often of an exaggerated type, while others caused osteoporosis. Still others resulted in the development of the peculiar lesion which has been called osteosclerosis. A study of the effect of these diets on the skeleton would indicate that the growth of the skeleton was dependent on at least three substances: (1) an organic substance present in certain fats, which is not identical with the antixerophthalmic fat-soluble A; (2) calcium; (3) phosphorus. If the organic factor is low in, or missing from, a diet, the structure of the osseous tissue is dependent on the ratio between the other ions in the circulating blood. If calcium is present in amounts equal to or exceeding those which would be optimal for growth and function, if all other factors are satisfactory but the phosphorus ion is low, rickets is produced. The same disease results when the converse relation exists between the two ions. In other words, diets which contain optimal or excessive amounts of calcium but are low in phosphorus and the organic element produce rickets. This is also produced from diets low in calcium and the organic element although phosphorus is present in satisfactory amounts. Diets which are satisfactory except that they are deficient in the organic substance result in osteoporotic but perfectly calcified bone. Diets which have a comparative deficiency in calcium but are very high in phosphorus and in the organic substance produce the so-called osteosclerotic bone, with large numbers of small trabeculae which are imperfectly formed. Diets deficient in calcium alone produce a pseudorachitic condition with overproduction of osteoid.

**Thymus Apoplexy.**—WAHL and WALTHALL (*Am. Jour. Dis. Child.*, 1922, 24, 27) report 2 cases which they classify as examples of this rather unusual manifestation of hemorrhagic disease of the newborn. The 2 cases were similar in many respects. Symptoms of meningeal irritation, lateral nystagmus, and generalized icterus were present in both babies. Labor was not normal, but was not unduly difficult or prolonged in either case. In both cases there was a marked increase in the coagulation time of the blood. In each case the necropsy showed a cerebral hemorrhage, inflammatory changes in the lungs suggestive of syphilis, and a diffuse hemorrhagic infiltration of the thymus in which the extravasation of the blood was both intralobular and interlobular, and was associated with suppuration necrosis and marked proliferation of the reticular epithelial cells. The cases differ in that the second case was much older than the first. The hemorrhages were more generalized in Case 1, and labor was more difficult. The immediate cause of death of this case was cerebral hemorrhage, while in the other bronchopneumonia was probably the more immediate factor causing death. There was a considerable organization of the hemorrhage in Case 2, indicating an older process than in Case 1 in which no new capillaries or fibroblasts were found. In both cases the Hassall's corpuscles were numerous, but in Case 1 they were dilated, and often contained a purulent exudate, forming early DuBois abscesses. On the other hand Case 2 showed a striking perivascular inflammatory reaction with swelling of the vascular endothelium, and also marked thrombophlebitis of the smaller veins. In Case 1 one of the large veins was partly occluded by a thrombus. The relation of these cases to syphilis is exceedingly interesting. Case 1 presented no positive clinical findings. The Wassermann tests on the bloods of both the father and the infant were negative. No examination of the mother's blood could be made. Several members of the family showed constitutional weakness and syphilis could not be excluded even with negative blood findings. The clinical findings in Case 2 were more suggestive of syphilis. The Wassermann test of the blood of the mother was strongly positive but in the case of the child was negative. There was no opportunity to repeat this test and a single negative test is not conclusive. The anatomic changes in both cases, while not pathognomonic, afford strong presumptive evidence of syphilis. The interstitial inflammatory changes in both lungs suggest syphilis. The lobules of the thymus that are not disintegrated by hemorrhage show changes in both cases that are regarded as characteristic of congenital syphilis. In both cases there was marked reticular epithelial cell proliferation, associated with more or less atrophy of the thymic lymphocytes, which has been noted by a number of authors as a characteristic change in the thymus of congenital syphilis. The etiology of thymus apoplexy is obscure. So few cases have been reported that final judgment cannot be made. It is probable that one or more of four factors play a part in each case. Circulatory stasis especially in the thymus in which marked hyperplasia exists may be a cause. When this is the main factor the hemorrhage is diffused throughout the gland giving the appearance of a hemorrhagic infarct. A second factor is trauma. A third factor is the presence of hemorrhagic disease of the newborn, that is, a defect in the coagulation mechanism of the blood. This hemorrhagic tendency



is frequently associated with, if not due to, some underlying infectious process analogous to hemorrhages in the medulla of the suprarenal so commonly found in the newborn. The fourth and probably the most important factor is the role played by infectious diseases, especially syphilis. It is common to find small petechial hemorrhages in the thymus in pneumonia in infants. Undoubtedly the hyperemia associated with an infection predisposes to hemorrhage. The fact that necrosis and suppuration preceded the hemorrhage in both of the cases reported, makes the presence of an infection, probably syphilis, most likely.

---

**Food Requirements in Newborn Infants.**—FABER (*Am. Jour. Dis. Child.*, 1922, 24, 56) thinks that appetite provides a fairly accurate index of the needs of the newborn infant. In his series of 85 cases and with the formulas he used it appeared also to be a safe guide in so far as the avoidance of dangers to the digestion is concerned. The demands of the infants for food exceeded the basal requirements on the second day, equaled the average total requirements of Benedict and Talbot on the third day. On the fifth day they rose to the Heubner optimum of 100 calories, and thereafter rose slowly to about 115 calories near the end of the second week. That these demands are not excessive is indicated by the weight curve which, avoiding a greater initial loss than can be accounted for by mechanical factors, showed the same rate of gain as was previously established for healthy infants in the same community. The author sounds a warning that the method he describes, adopted for a special purpose, is not advocated for general use with breast-fed infants. It may be well that for the conservation and increase of mammary secretion a period of partial starvation during the first weeks is useful or even necessary.

---

**The Food Requirements of Children: Carbohydrate.**—HOLT and FALES (*Am. Jour. Dis. Child.*, 1922, 24, 44,) continue the investigations of the food requirements of the young in a study of the carbohydrate requirement. They found that carbohydrate is a desirable and probably an essential component of food for children, although it does not have any specific function in nutrition. It forms the largest part of the diet of all periods of life. Nursing infants take on an average of about 12 gm. carbohydrate per kilogram of body weight daily. Artificially fed infants usually receive somewhat more than this. The carbohydrate in the diet of an infant is almost entirely sugar, that of the nursing infant entirely lactose and that of the artificially fed infant usually a mixture of lactose with saccharose or maltose and dextrin. The carbohydrate intake of more than one hundred healthy children from one to eighteen years of age, studied by the authors, averaged 10 gm. per kilogram. Of this, 51 per cent was sugar, including lactose, saccharose and fructose, and 49 per cent was starch. Carbohydrate is more economical than fat or protein, both commercially and physiologically. Because of the first-named advantage, there is a growing tendency to increase the proportion of the carbohydrate in the diet beyond the amount which is desirable. When a very large proportion of the food is in the form of carbohydrate, the intake of fat and protein or both is likely to be less than the normal nutritive need of the body. A diet excessive in carbohydrate leads to an abnormal deposition of fat

and without a corresponding increase in muscular development. Children taking such a diet have a feeble resistance to infection. There is no evidence that a relationship exists between the high proportion of the carbohydrate in the modern diet and the prevalence of dental caries. Definite digestive disturbances, chiefly intestinal, may be produced when the carbohydrate in the diet is excessive. There may result increased fermentation with loose acid stools or constipation with flatulence and abdominal distention. When long continued these disturbances are very difficult to control. Carbohydrate furnishes the calories needed in the diet which are not supplied by the requisite amounts of fat and protein. It seems rational to allow in the diet of the child of average activity about 12 gm. of carbohydrate per kilogram of body weight at one year, decreasing this amount to about 10 gm. per kilogram at six years and maintaining it at this value throughout the remainder of the growth period. An increase in the total caloric need may be supplied by the carbohydrate alone.

---

**Gastric Findings in Children with Anorexia.**—SAUER, MINSK and ALEXANDER (*Jour. Am. Med. Assn.*, 1922, 79, 184) observed that the average emptying time of the stomach for twelve children with good appetite was four and a half hours. In twenty-one children with poor appetite the emptying time was six and one-tenth hours. The stomachs of the twelve children first mentioned were empty in five hours while in the other group sixteen still had retention at the end of five hours. All but one of the twenty-one children with poor appetite had an original emptying time longer than that found to be the average for the children with good appetites. The average total hydrochloric acid for the twelve children with good appetite was 61.2, the free acid was 26.3. For eighteen with poor appetite the total acid was 49.4, and the free acid 14.9. In two children of the group with poor appetite, free acid was absent on examination and upon reëxamination months later, while their emptying times were not especially long. Eleven of the twelve children of the first group were of the sthenic habitus. Sixteen of the twenty-one children of the other group were of the hyposthenic or asthenic habitus. In a number of asthenic children, the emptying time of the stomach and the amount of the acid were influenced beneficially by proper measures and this was reflected by an increase of appetite and weight.

---

**The Difficulties and Practicability of Infant Feeding in a Country Practice.**—SIMPSON (*Penna. Med. Jour.*, 1922, 25, 782) sums up the difficulties as superstition, ignorance, the fancied self-sufficiency of mothers of large families and the absence of ice and clean milk. It will be remarked that many of these difficulties are not limited to the country practice. He points out that there is one definite superstition, which is found chiefly among the Pennsylvania Dutch, and which is applied to malnutrition, rickets, or any chronic disease characterized by loss of weight or failure to gain weight. Such conditions are all spoken of as the "take off," and often long before a physician is consulted such a case is "powwowed" or measured with a tape by some member of the laity, who is supposed to be able to cure this condition, which is looked upon as a mysterious disease that no method of feeding or medical treatment can cure.

## OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

**Concealed Hemorrhage Complicating Pregnancy.**—WILSON (*Surg., Gynec. and Obst.*, 1922, 34, 57) describes a case of albuminuria and edema in a pregnant hospital patient, from whom a clear history could not be obtained. After a gestation period of about seven months, there was a shoulder presentation and heart sounds could be made out on the right side of the abdomen, comparatively low. On estimating the size of the mother, it was found that the pelvis was a little under the average. The patient was admitted to the hospital for the treatment of toxemia and grew considerably better. When labor came on, uterine contractions were vigorous, and after several hours of labor there was vaginal hemorrhage with vomiting, nausea and epigastric pain. This became very severe, with tenderness on palpation, and shock and hemorrhage, which steadily increased, and there was pronounced pain on palpating the abdomen, and when the uterus was palpated it did not relax but seemed to be in tonic contraction. The size and location of the child could not be made out but a presenting part seemed to be at the brim of the pelvis. It was impossible to hear the heart sounds. There was no evidence of labor, no dilation of the cervix, and on introducing the finger a placenta could not be felt. It seemed evident that the placenta was more or less loosened. Section was undertaken as soon as possible, and on opening the abdomen a serous, bloody fluid was found in abundant quantity. The appearance of the uterus was unusual, as it was dark bluish-black in color, with areas of different appearance; this abnormality being most pronounced at the left upper portion. On examining the uterus more carefully both anterior and posterior walls presented this unusual condition. Extending in a longitudinal direction there were depressions in the uterus where the muscular tissue had separated without involving the peritoneum. There seemed to be no abnormality in the ovaries and tubes. When the uterus was incised on the left side, the afterbirth was found in front and loosened from its attachment, so that but two-thirds of the placenta was still attached. There were several pints of fluid blood in the uterine cavity and a considerable quantity of clot. It was possible to extract through the abdominal wound the entire fetal mass without rupturing the membranes. The operator did not perform a hysterectomy, and as the patient showed some shock, salt solution was given hypodermically. Unfortunately abortion was unsuccessful and had been undertaken too late, the patient surviving but a few hours. A postmortem examination revealed considerable change in the substance of the liver,

which was less firm and lighter in color than the average. The gall-bladder, bowels and stomach seemed normal, but there was some softening in the spleen. The kidneys resembled the liver in the lighter color and softer consistency. The tubes and ovaries were normal, but over the surface of the uterus, under the peritoneal covering, blood had extravasated and a similar condition was present in the left broad ligament. On sectioning the uterus, its muscle was found entirely lacking in tone and firmness, and there were degenerated areas between the individual muscle fibers. On microscopic examination of the liver lobules, necrosis had advanced to a considerable degree in the center of each lobule. This was shown by the staining and by beginning fatty degeneration. A similar process had involved the kidneys and also the uterine muscle. In the latter, blood had been exuded in considerable quantity amid the muscle fibers. On gross examination there was nothing abnormal in the placenta. In the villi hyaline degeneration was present in no very marked degree. In addition to and including his own, the author reports 69 cases. The theory that concealed hemorrhage and separation of the placenta arise from mechanical violence to the uterus, he discards, nor does he accept uterine distention or hyperemia of the wall of the uterus as a sufficient cause for separation of the placenta. The theory that failure of the uterus to permit escape of blood causes placental separation is not adequate. For some time there has been developing a tendency on the part of obstetricians to consider the toxemia of pregnancy as the essential element in producing the condition under discussion. If we are to rely upon the teaching of pathology, there is a remarkable likeness between the condition of the tissues in these cases and that seen in the bodies of animals dying from the bites of serpents. It has long been known that in many patients eclampsia has preceded accidental hemorrhage. Hence, it is at once suggested that an important factor is common to both and that high blood-pressure may be a common cause. So far as the recovery of the patient is concerned, there must always be a considerable mortality and morbidity. The writer gives a death-rate of 38 per cent in 50 patients under observation, in whom he made a diagnosis before operation of the condition. A complication so grave must greatly increase the chance of fetal death, and in 67 cases under the observation of the writer the mortality was 92.5 per cent. It must not be concluded that death inevitably follows the accidental separation of the placenta in all cases, nor that all patients who have this complication require abdominal section. Where, however, there is evidence of considerable disturbance in the patient's pulse, temperature and respiration, operation should be done as soon as possible. The majority of observers agree that Cæsarean section is the preferable operation. Hysterectomy should never be done unless the conditions present imperatively demand it and the preservation of the uterus would increase the risk to the mother's life. Many of these cases show a tendency to continue to bleed after the uterus has been emptied. In many others there must be a supposition that infection

is present. Under these circumstances the operation known as the Porro hysterectomy is safest. The writer's study of the subject has led him to believe that what he terms apoplexy of the uterine and placental tissues results from the abundant discharge over the endometrium and in the substance of the uterus of a toxic material which forms during hemorrhage. This substance seems to be produced by the placenta and hence the tissues at the site of the placenta are most often attacked. That variety of bleeding which sometimes occurs, and in which it may be impossible positively to demonstrate the cause of the complication, is considered by the writer to be a part of the same process. In many cases so badly weakened is the wall of the uterus by these toxins that bleeding occurs into the abdominal cavity, and also from the uterus after it has been emptied. In those cases where the complication develops rapidly without dilatation of the cervix or labor, and where evidently the bleeding is severe, there is no choice of method but Cæsarean section, with total extirpation of the uterus or hysterectomy, as indicated.

---

**The Condition of the Membranes and Especially the Epithelia of the Amnion in Cases of Premature Rupture of the Membranes.**—HEINLEIN (*Monatsschr. f. Geburtsh.*, 1922, 56, 237) alludes to an account, already published, giving the examination of the membranes in cases of premature rupture where it seemed evident that a violent inflammation of the amnion and chorion, causing necrobiosis, was possibly the cause of the premature rupture. Cervical endometritis was evidently the cause of the inflammation preceding the rupture of the membranes. The writer has studied 27 cases of premature rupture of membranes, and 12 cases of membranes ruptured at the usual time, to observe the microscopic condition in both: His investigations came practically to the same conclusion as those already quoted. In the 27 cases there was an active inflammation of the membranes with destruction of cells in 5 cases. The process was less active and severe in 9, but feebly developed in 4; while there was considerable hemorrhage in the deeper layers of the membranes, with or without inflammation, in 7 cases. In 2 cases no pathological condition could be found, although there was a considerable deposit of cellular material, which made it hard to find the site of the rupture. It is important to find the point of rupture, because the pathological process is most active at that point. As one proceeds further away from the point of rupture in the membranes the pathological process becomes more or less indistinct. This seemed to disappear in the vicinity of the placenta where the membranes join the afterbirth. Only in those cases where the primary rupture of the membranes occurred near the border of the placenta did the characteristic pathological changes appear, and occasionally this inflammatory process attacked a small portion of the placenta. A genuine inflammation of the placenta with small cell infiltration, in or between the villi, was not observed. The writer recognized the amnion and the layer of cells beneath the chorion, which often contains degenerate villi and other remains of the decidua. Where inflammation was most pro-

nounced the structure of the membranes could not be made out, and the tissues normally present were replaced by small homogeneous masses without nuclei. At other portions necrosis was evidently present with round-cell infiltration and leukocytes and the epithelium of the amnion had practically disappeared. The degree of necrosis depended upon the violence of the inflammation. Where the inflammation was but slight its site was in the tissues between the amnion and chorion. Bleeding was present in a few cases only, and in some where hemorrhage was most copious there was no evidence of inflammation. The site of bleeding was usually the decidua. Near the tissue the bloodvessels were dilated and increased, and the walls of the vessels were so thinned that in some places they could not be recognized. The blood made its way between the layers of the membranes. In some cases blood pigment was present, but this is sometimes seen in normal cases. In some cases of inflammation of the chorion and amnion, these were attacked before the epithelium of the amnion was inflamed. In other cases masses of granular material were found above the epithelium of the amnion; the cells were not only greatly altered but in some places had disappeared with the development of cylindrical epithelium in masses with wide spaces between. Where necrosis occurred the nuclei had disappeared and the form of the epithelial cells could not be made out. In 25 of the 27 cases in which the membranes had ruptured prematurely there was a very essential change in the membranes. This change was an inflammation (recent or of some duration) with a necrotic process often accompanied by hemorrhage, hemorrhage being sometimes present without inflammation. This process was usually seen in the layers underneath the chorion, while hemorrhage usually occurred in the decidua. In all cases the epithelium of the amnion was affected. It seems evident that these changes in the membranes have something to do with premature rupture and that the integrity of the amnion depends upon the condition of its epithelium. The epithelial cells are usually firm and resisting and influence the formation of the fibers of the amnion. It will be remembered that the amnion has no bloodvessels and that it is nourished from the deeper tissues beneath. If a pathological process attacks these deeper tissues the epithelium of the amnion will immediately suffer, the fibers of the amnion are not properly formed and the membranes will rupture without especial violence. One can readily appreciate that, if the membranes rupture sometimes before delivery, bacteria may make their way into the uterus and set up an inflammation of the membranes; but in some cases the time between the rupture of the membranes and delivery is too short for these changes to occur. The changes in the membranes must have taken place by some previous process. In a case of abortion at four months the embryo was removed with unruptured membranes from the uterus. Microscopic examination of the membranes showed a severe inflammation throughout the entire membranes with extensive necrosis. As to the existence of a previous endometritis the writer is unable to make a positive statement. As slight inflammation of the decidua is often found in membranes otherwise normal, what the element is which

extends this inflammation to the layer between the chorion and amnion is not clear. An inflammation of the placental substance itself with small-cell infiltration and infiltration between the villi of the chorion could not be clearly demonstrated in any case.

---

## GYNECOLOGY

---

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY  
OF PENNSYLVANIA, PHILADELPHIA.

---

**Action of Salicylates on the Uterus.**—Many text-books of pharmacology mention that abortion sometimes occurs during the treatment of acute rheumatism with salicylates, but that it is uncertain which of these factors is the cause. Therefore in order to determine more definitely the relationship existing between the drug, the disease and abortion, GUNN and GOLDBERG (*Jour. Pharmacol. and Exper. Therap.*, 1922, 19, 207) performed experiments which showed that salicylate of soda has a definite stimulating action on the uterus, but that this action is not powerful; for instance, on the isolated uterus it is only half as strong as sodium carbonate and possibly less than one-fortieth as strong as quinine hydrochloride. It was noticed that when large doses were gradually introduced into the blood, as occurs when salicylates are given therapeutically by mouth, the stimulation of the uterus was much less marked. The stimulation did not appear to these investigators to be so pronounced as to suggest that it is likely to be of any great importance in the production of abortion, however, when salicylates are administered clinically very wide variations are found in the amounts given before toxic symptoms appear, and it is not impossible that there may also be considerable differences in the amounts necessary to influence the uterus. Acute rheumatism is practically universally treated with salicylates and these investigators conclude that if salicylates had a greater abortifacient action than their experiments show, the incidence of abortion in rheumatic fever would be greater than it is. In fact since the effect of salicylates is so apparent on rheumatic fever and so slight on the uterus, it is possible that the reason why fewer miscarriages are seen in rheumatic fever than in the other acute fevers is because of the rapid control of the former by sodium salicylate.

---

**Effect of Radiation on the Blood.**—The results of the analysis of the experiments performed by LEVIN (*Am. Jour. Roentgenol.*, 1922, 9, 112) to determine the action of radium and roentgen rays on the blood and

the blood-forming organs tends to confirm the prevailing opinion that the lymphocyte is the most radio-sensitive cell in the animal organism. The change in the numerical relationship of the two types of white cells was not accompanied by a noticeable change in the total leukocyte count. Apparently the mechanism of the action of the rays on the leukocytes of the blood consists in the destruction of the lymphocytes, which is then followed by the release of the polymorphonuclear leukocyte from the bone marrow or by an overproduction of this type of cell by the blood-forming organs. Certain investigators maintain that the polymorphonuclear leukocytes are the type of the blood cells most readily destroyed by the rays. However, the analysis of their results shows that the destruction of the polymorphonuclear leukocytes only takes place as the final result of the action of a lethal dose of the rays which produces ultimately a severe general leukopenia. In the present investigation however, only such amounts of radium and roentgen-ray were given that the animals could completely recover after the lapse of a certain time and the blood picture again become normal. The most important phenomenon observed in the course of this study is the difference with which the two species of animals, the frog and the rabbit, react to the action of radium and the roentgen-ray. In the frog the same general effect was obtained on the blood by the amount of roentgen raying employed in this investigation, as well as by the insertion of a glass capillary containing 1.0 to 9.6 millieuries of radium emanation. The blood of the rabbits reacted to the roentgen-rays in a manner identical with that of the frog. On the other hand, an insertion into the spleen or the bone marrow of a rabbit of 2 or 4 capillaries, that is, 2 or 4 times the amount of radium emanation inserted into the frog, produced no change in the blood of the rabbit, though it produced marked local effect on the spleen and bone marrow. These comparative findings in the two species of animals and the two types of radiation are of considerable importance to the subject of radiotherapy from the two following standpoints: The subjects of the relative therapeutic efficiency of radium and roentgen-rays of the higher or lower voltage of the electric current producing the roentgen-rays, of the correct methods of physical measurements of the rays, whether photographic or ionization methods, for instance, and the correct amounts to be used, are in the order of the day. However, these subjects are treated chiefly from the standpoint of physics rather than from that of biology. There cannot be any doubt that measured by photography and ionization methods or generally considered from its physical aspect one roentgen-ray application as employed in the present investigation and one capillary tube containing 1.0 (or less) millieuries of radium emanation inserted into the frog and left there to decay represent two qualitatively and quantitatively different entities. Nevertheless they must be considered quite analogous biologically, since they produce the identical effect on the blood of the frog. This indicated clearly that for biology and medicine a biological standard of measurement would be of far greater value than the physical methods. It may be added that the action of the rays on normal blood and lymphoid tissue is of greater importance than their action on the skin, the more so that the radium and roentgen-ray burns are most probably due to the change in the lymphoid tissue of the walls of the bloodvessels. The second phenomenon observed in



this investigation further illustrates the importance of the biological differences for the ultimate result of the action of the rays. The roentgen-rays produce a change in the blood picture of the rabbit because the square surface of its body is greater than that of the frog, and consequently the former receives a greater amount of radiation, though all the other conditions of the roentgen-ray apparatus were the same as those used in the frog. The radium emanation tubes produced no change in the blood of the rabbit, though the amount was more than sufficient to produce a change in the blood of the frog. The reason for it lies in the fact that the effect is distributed in the larger quantity of the blood of the rabbit and becomes so small as not to be perceptible. At the same time the local effect of the radium emanation is very marked. Two conclusions may thus be drawn from the analysis of the experiments. First, that radium, as compared with roentgen-rays will produce the same and even a more marked local effect with far less general disturbance of the blood. Second, that the larger the square surface of the entry of the roentgen-rays into the organism the more severe is the general effect on the blood.

**Trichomonas Vaginalis Vaginitis.**—The presenting symptom of trichomonas vaginalis vaginitis, according to the experience of HARTWELL (*Colorado Med.*, 1922, 19, 86), is a vaginal discharge which is so irritating as to be "scalding" to the skin with which it comes in contact and so profuse as to necessitate the wearing of a napkin; it is so perversely persistent as to fail to respond to ordinary measures. The scalding of the skin is often so severe that the patient is handicapped in the performance of her duties by day and the associated pruritus is so intense that her night's sleep is disturbed. During the menstrual period however, the irritation and itching usually subside. In addition to this the discharge is frequently so malodorous that it interferes with the patient's social activities. When a patient presenting these symptoms is examined it is often noted that the skin on the inner aspect of the thighs and over the perineum is reddened, if not eroded, by the irritating vaginal discharge. On spreading the labia the vestibule is usually bathed with a thin white secretion and the mucous surfaces of the labia minora and the carunculae myrtiliformes may present minute bright red macules, while occasionally small condylomata stud the labia. When the speculum is introduced, there is seen in the vault a quantity of puriform secretion notably full of bubbles, and this secretion may be superlatively malodorous. On removing it, the vaginal mucosa presents the beefy red appearance of any vaginitis if the process be acute, or is quite normal in color if the process is chronic. In either case however, the characteristic raised papules, irregularly scattered over the mucosa are in evidence. They may be solitary or aggregated in small groups and not infrequently the apices of the papules are eroded, presenting superficial ulcers of small size which may bleed. The appearance presented by the vaginal mucosa is strongly suggestive of a dermatitis produced by a chemical irritant such as iodine, or the early lesions of a herpes zoster. The reaction of the vagina is very strongly acid. Such appearances are almost pathognomonic of a trichomonas vaginalis vaginitis, but the diagnosis is confirmed by the microscopic examination of a small bit of the bubbly secretion when large numbers

of motile flagellated trichomonades are easily recognized. In treating this condition, HARTWELL has obtained the most satisfactory results by placing soda bicarbonate powder in the vaginal vault. The following morning the patient takes a douche of plain water. In the afternoon the treatment is repeated. Daily treatments are required for about two weeks and every second day for another four weeks before the vagina is free from trichomonades. The principle of the treatment is to maintain the reaction of the vagina strongly alkaline, which alkalinity seems to be inimical to the life and growth of the trichomonas vaginalis.

---

## PATHOLOGY AND BACTERIOLOGY

---

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

---

**Complement-fixation Tests in the Diagnosis of Tuberculous Infections.**—The results obtained by various investigators, employing the complement-fixation test in tuberculous infections have not been concordant and observers have differed from each other in the percentage of positive findings in cases of definite tuberculosis, as well as in their views concerning the diagnostic and prognostic value of the test. Realizing that such divergencies can be attributed in part to differences in the technic used, SELLERS and RAMSBOTTOM (*Jour. Path. and Bacteriol.*, 1922, 25, 247) conducted numerous complement-fixation tests on the blood and spinal fluid of adults and the blood of children with and without clinical evidence of tuberculosis, and obtained results which agreed, on the whole, with those of other observers. Seven different strains of tubercle bacilli were used for preparing five antigens found useful by other workers. Accordingly, 3 of these antigens were employed in comparative tests on 40 adult cases of pulmonary tuberculosis which yielded from 75 to 90 per cent positive according to the antigen, 40 cases of bone tuberculosis, where 50 to 55 per cent were positive and 15 cases of non-syphilitic spinal fluids in which the positives varied from 6 to 33 per cent. Varying percentages of negatives were encountered in undoubted cases of tuberculosis and a few non-tuberculous sera gave positive reactions. Moreover, nearly one-half the cases of syphilis in children in which there was no clinical evidence of tuberculosis gave a positive tuberculosis test. In 13 cases of non-tuberculous spinal fluid, 4 were positive and 9 negative; in 12 cases of meningitis in which there was a suspicion of a tuberculous origin, 6 were positive and 6 negative and in 11 cases of tuberculous meningitis, all were positive. As a result of their investigations, the authors "are not satisfied that

complement-fixation tests afford a reliable means of clinical diagnosis in tuberculosis cases." They believe that "too little attention has been paid to the so-called non-specific reactions." They think, however, that possibly complement-fixation tests may throw some light on the pathology of tuberculosis.

---

**The Fat of Adipose Tissue in Malignant Disease.**—Following the observations of Duncan that a decided difference existed in human fat before and after puberty, the low percentage of 4.47 of non-saturated fatty acids between nine and eleven years of age being replaced by the higher one of 60.88 from sixteen to nineteen years, and that a similar increase takes place in the fat of cancer patients (the percentage rising from 61.1 in health to 72.62 in that disease), CURRIE (*Jour. Path. and Bacteriol.*, 1922, 25, 213) investigated the condition of the fatty tissues in cancerous patients and the presence, or otherwise, of any pigments or special pigment in it and cancerous tissue. Iodine values were determined in 33 specimens of fat, of which 8 were from sarcomata, 21 from carcinomata and 2 were from chronic inflammatory lesions and 2 from normal cases. Although Duncan found that the adipose tissue fat in cancer, no matter in what part of the body it was stored, exhibited a constancy in iodine value, the present work indicates that unsaturation finds its highest expression in fats adjacent to carcinomata with sarcomata coming next, whereas there is a constancy in iodine value of normal adipose tissue fat from any part of the body. It was found "that the hydrogenation of fat varies inversely with the degree of pigmentation, the pigment probably acting as a catalytic inhibitor, so that if the fat is highly pigmented and also highly unsaturated it exhibits a greater slowness in adjusting itself to corresponding body conditions than if the degree of pigmentation were lower. Adipose tissue is at any moment in delicate equipoise, two opposed and balancing reactions (saturation and unsaturation) proceeding simultaneously, the net result being dependent on the concentration of the respective enzymes."

---

**Further Investigations of Disturbances of Blood-sugar Equilibrium in their Relation to Neoplasia.**—Working with rats, ROHDENBURG, KREHBIEL and BERNHARD, (*Jour. Cancer Research*, 1921, 6, 223) by ablating the various endocrine organs as kidney, thyroid, thymus, spleen, adrenals, pancreas, testes or ovaries either singly or in all two gland combinations and determining the blood-sugar values after injection of a 1 per cent heterologous protein (beef peptone) in doses of 0.5 cc or by previously inoculating extracts of liver, pituitary, pancreas, adrenal and thyroid in another group, found that the disturbance of blood sugar equilibrium which follows the injection of a protein varied in intensity and type; that the removal of certain of the endocrines influenced both the intensity and type of the reaction and that neither the intensity nor the type of the reaction had any relation to the strength of the antibody development after the injection of the selected protein. With the idea of clinical application, a large series of human beings, suffering from various diseases, were injected with homologous proteins (blood serum or ascitic fluid) and the sugar content of the blood was ascertained. It was learned that in diseases involving the gastro-

intestinal tract, duodenal ulcer excepted, and in diseases involving the gall-bladder and liver 88 per cent of all cases of neoplasia showed a reaction of less than 12 mgm. The authors indicate that, if the endocrine relationship which they outlined in the first part of their investigations be accepted, such a lessened reaction would suggest, either spleen, adrenal or gonad insufficiency, or thyroid, adrenal or pancreas over-activity. They believe that the observation concerning the blood-sugar equilibrium in gastro-intestinal neoplasia is possibly of value as a diagnostic procedure.

---

**The Supposed Importance of Vitamins in Promoting Bacterial Growth.**—McLEOD and WYON (*Jour. Path. and Bacteriol.*, 1921, 24, 205) investigated the relations, if any, which existed between vitamins and bacterial growth with a view to use the bacterial growth as an index of the presence of vitamins in research upon the latter. The effect of materials containing "water soluble B" upon *S. aureus* and *B. dysenteriae* (Shiga) was determined by the use of a simple phosphate-agar medium to which the various extracts and chemical substances had been added. Many of the results were compatible with the vitamin hypothesis. There was a large discrepancy between the two guinea-pig kidney extracts, seemingly due to an unknown inhibitory substance in one of them. The figures for bran and milk were very low. The same of milk was of the "separator" type and possibly inhibitory substances were present. Comparison of amino-acid content with potency negatived the idea that the results were entirely due to amino-acids and the suggestion that nucleic acid or its congeners were responsible for the results was not substantiated by experiment. A comparison of the chemical and physical properties of the staphylococcus stimulant of yeast with those of "water soluble B" revealed serious discrepancies. An attempt was made, also, to determine the nature of the property of fresh blood or serum by virtue of which it promoted the growth of delicate bacteria, such as pneumococcus and meningococcus, by inoculating a series of tubes of bouillon to which additions of blood, serum and other substances had been made from dilute emulsions of the bacteria. It was learned that the growth promoting power did not bear any definite ratio to the known vitamin contents and that this growth promoting power for pneumococci was to some extent destroyed by heating serum, etc., whereas that for meningococci was altered but little or enhanced. It was also found that the growth promoting quality of 1 per cent peptone agar plus serum was very little enhanced by the addition of tryptic digests where pneumococcus, meningococcus and hemolytic streptococcus were concerned and that high concentrations of amino-acid readily inhibit the growth of these organisms. On the other hand, tryptic digests favored the growth of the bacteria of the bowel. No satisfactory evidence that the growth promoting factor for bacteria can be extracted by alcohol could be obtained, the power of promoting growth inherent in the serum being, apparently, a phenomenon of the colloid state.

---

**The Diurnal Variation in the Sizes of Red Blood Cells.**—PRICE-JONES (*Jour. Path. and Bacteriol.*, Cambridge, 1920, 23, 371) found that there was a gradual increase in the diameter of red cells during the day

and a diminution during the night; that violent exercise increased these changes, whereas gentle exercise had no apparent influence; that rest in bed did not abolish the diurnal variations and that after forced breathing the diameters of the red cells were diminished. The method of examination consisted in making films from blood obtained by pricking the finger or ear, drying in the air without heat, fixing and staining in Jenner stain for two minutes and afterward for two minutes in a weak aqueous solution of eosin. Some convenient form of projection apparatus was then arranged to project the image of the microscopic field on to a sheet of paper lying on the table and adjusted for a magnification of 1000 diameters. The red cells were outlined in pencil, two diameters (maximum and minimum) were measured to 0.5 mm. and the mean of these measurements was accepted as the diameter of the cells. The cells were classed into groups, progressing by  $0.25\ \mu$ , and the mean diameter of 500 cells was taken to represent the mean diameter of the red cells for any specimen of blood. The author states that his observations "suggest that the variations in size of the red cells are due to differences in the reaction of the blood, but whether the diminished alkalinity and increased diameters which prevail during the active part of the day are due to accumulation of  $\text{CO}_2$  or lactic acid, or to some other source of altered reaction, we have at present no means of judging."

---

**The Carbohydrate Metabolism of Surviving Mouse Tissues and Tumors.** — RUSSELL (*Brit. Jour. Exper. Path.*, 1922, 3, 51) reports a continuation of his previous work with Woglom, (*Ibid.*, 1920, 1, 244) having to do with the gaseous exchange of surviving tissues of the mouse and particularly the determination of the ratio of carbonic acid output to oxygen intake, that is, the respiratory quotient. By measuring the changes in volume observed in an air space containing a known quantity of finely divided tissue or tumor, it was found that significant differences occurred in normal kidney, liver, breast, submaxillary gland and embryo and still greater differences were encountered in six strains of transplanted tumors, the respiratory quotient of the more rapidly growing tumors being higher than that of the more slowly growing ones. By adding small amounts of different sugars to the tissue emulsion before placing it in the respirometer bulb, it was ascertained that "the low respiratory quotient observed with slowly growing transplanted tumors was not attributable to their incapacity of burning glucose; that mouse tumors and tissue appeared capable of dealing with the common sugars in a very similar manner, provided the sugars were supplied directly and that differences in the quantity of sugar within the cells was a probable explanation of the variations in the carbohydrate metabolism of tumors growing at different rates."

---

**The Histology of Destructive Changes in Icteric Livers.**—In a histological study of the livers from 7 human cases of grave mechanical jaundice, which furnished convincing illustrations of destructive changes caused by the retention of bile, SCHWARZ (*Jour. Path. and Bacteriol.*, 1922, 25, 207) found that the stasis produced a dilatation of the biliary capillaries with tearing in the inter- and intracellular endings of the fine biliary vessels. The liver cells showed only slight degenerative metamorphoses as long as the thrombi formed only casts within the capil-

laries. After these latter burst, the thrombi became coiled up and part of the bile diffused into the surrounding tissue. It was thought improbable that these distorted thrombi fused into the large golden yellow lumps of bile found next to the trabeculae but that they probably were formed within the trabeculae when the latter were rapidly destroyed by polycholia combined with obliteration of biliary ducts. The portions destroyed by the larger clumps of bile with subsequent imbibition of the tissue usually exhibited remnants of pigment in the detritus cavities. There was hardly any leukocytic infiltration nor many marked extravasation for blood because of the rather slow destruction which seemed to permit of extensive regeneration. As soon as a few cells were destroyed they were replaced by new ones. The production of connective tissue between the acini was apparently initiated by fibroblasts, although it was not clear that a regular granulation tissue was a forerunner of the connective tissue strands. No actual enclosure of biliary thrombi in phagocytic cells could be observed.

---

#### The Production of Coliform Infection in the Urinary Tract of Rabbits.

—In order to produce lesions in the kidney by intravenous injection of coliform organisms, so as to examine the inflammatory changes produced soon after infection so that the path of the bacilli through the kidney might be studied, LEPPER (*Jour. Path and Bacteriol.*, 1921, 24, 192) performed a series of experiments upon rabbits by injecting various strains of *B. coli communis*, *B. coli communior* and *B. acidilactici* into the ear vein in different dosages with and without complete obstruction to the urinary flow by ureteral ligation over varying lengths of time. When the coliform bacilli appeared in the urine after intravenous injection, there was, with one exception, evidence of concomitant kidney changes as shown by the presence of albumin, or pus, epithelium and bacilli in the urine. The sequence of events following intravenous injections, so far as they could be traced in microscopical sections, was first, a bacillary embolus of capillary vessels, generally those of the papilla, followed by a round cell infiltration in the connective tissue surrounding the affected vessels. If the infection was severe, the inflammation extended to the tubules and in some cases necrosis of the tip of the papilla occurred. The complete obstruction of the urinary flow from a kidney for so short a period as fifteen minutes was adequate to make it vulnerable to coliform organisms circulating in the blood. The mode of production of these lesions was probably hemorrhage into the kidney from dilated veins caused by pressure of the distended pelvis on the renal vessels. There was some evidence that the type of inflammation resulting from blood infection combined with obstruction to the urinary flow was more severe than that produced by blood infection alone. Severe infections of the connective tissue in the vicinity of the kidney did not spread very rapidly to that organ, but if a blood infection resulted from the septic focus a renal lesion sometimes followed.

---

**Experiences with the Schick Test and Active Immunization Against Diphtheria.**—COPEMAN, O'BRIEN, EAGLETON and GLENNY (*Brit. Jour. Exper. Path.*, 1922, 3, 42) continued investigations into the value of the Schick test and active immunization against diphtheria upon the personnel of an institution where the population was a very stable one.

Of 329 children between the ages of three and sixteen years, among whom a recent epidemic of diphtheria had occurred, 18 (6 per cent) carried morphological *B. diphtheriæ* in throat or nose. At the end of the epidemic 5 per cent carriers were found which decreased to 2 per cent, two months later. Twelve cultures of the 18 children were isolated, 5 of which were virulent. The authors believe that the avirulent carrier is of no epidemiological importance and that the danger of a carrier of virulent bacilli is proportionate to the number of virulent organisms present in throat and nose, and therefore, to the ease with which the virulent bacilli can be isolated. Of the 329 children, 102 (31 per cent) gave a positive Schick reaction. Ninety-five per cent of the readings made on the first day were accurate. Of 203 children who were retested two months later, 201 gave the same reaction. Ninety-eight per cent of 102 Schick-positive children who received toxin and antitoxin mixture, gave negative or negative and pseudo reactions eleven weeks later.

---

## HYGIENE AND PUBLIC HEALTH

---

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

---

**Investigations on the Control of Hookworm Disease. I. General Introduction.**—W. W. CORT (*Am. Jour. Hyg.*, 1921, 1, 557) in this paper gives an analysis of some of the factors involved in hookworm control and points out some of the unsolved problems in connection with the life of the hookworm in the soil. He emphasizes the following conceptions: (1) That the object of hookworm campaigns is rather to reduce the number of worms in a population than to cure individuals completely, (2) that the factors involved in the spread of hookworm disease in different situations are so complex and differ so in different localities that each control project must be considered as an independent problem, and (3) that an adequate study of the sources of human infestation in an area will aid greatly in the development of control measures. The author further points out that little is really known of the life of the hookworm outside the body in its natural environment on account of the difficulty of studying the larvæ in the soil. The development of an apparatus by Baermann which makes it possible to isolate hookworm larvæ from the soil makes it possible to attack effectively a number of problems on this stage. An outline is given which suggests a number of lines along which investigations need to be directed in the study of the life of the hookworm outside the body.

**II. The Description of an Apparatus for Isolating Infective Hookworm Larvæ from Soil.**—W. W. CORT, J. E. ACKERT, D. L. AUGUSTINE and FLORENCE K. PAYNE in this paper (*Am. Jour. Hyg.*, 1922, 2, 1-16) make their first report of investigations carried on in Trinidad, British West Indies, on hookworm disease under the joint auspices of the Department of Medical Zoölogy of the School of Hygiene and Public Health of Johns Hopkins University and the International Health Board of the Rockefeller Foundation. It gives a description of Baermann's apparatus as used in the work of this expedition, an account of the results obtained in isolating hookworm larvæ from the soil with this apparatus under a variety of conditions, and some suggestions as to how it can be utilized in hookworm investigations and control work. By the use of the apparatus as described in this paper it was possible to isolate nematodes from considerable quantities of soil. It was found to be possible to distinguish mature hookworm larvæ both sheathed and unsheathed from other nematodes found in the soil, by their characteristic structure and movement. Experiments to standardize the apparatus showed: (1) That to isolate a satisfactory percentage of the larvæ the water must be warmer than the soil, (2) that a slightly higher percentage of the larvæ present can be isolated from moist than saturated soil, (3) that a larger percentage of the larvæ can be isolated from coarse soil than from that with finely divided particles, and (4) that while most of the larvæ escape from the soil in the first six hours an appreciable percentage come out after this time.

---

**III. A Discussion of the Finding of Unsheathed Hookworm Larvæ in the Soil.**—W. W. CORT, D. L. AUGUSTINE, J. E. ACKERT, FLORENCE K. PAYNE and G. C. PAYNE (*Am. Jour. Hyg.*, 1922, 2, 17) report the finding that a large proportion of the mature hookworm larvæ isolated from soil samples brought in from infested spots in the field and from experiments in soil had lost their protective sheaths. The conclusion is reached that it is a common thing for mature hookworm larvæ to lose their sheaths and to continue to live in the soil. This finding will probably make it necessary to revise many of our conceptions in regard to the life of the infective hookworm larvæ in the soil since it was thought always to live enclosed in a sheath.

---

**IV. The Relation of the Domestic Chicken to the Spread of Hookworm Disease.**—On account of the extent to which the domestic chicken ingests human feces, especially under tropical conditions, its relation to the spread of hookworm infestation is a matter of considerable importance. J. E. ACKERT (*Am. Jour. Hyg.*, 1912, 2, 26) studied this problem experimentally and found (1) that eggs of the human hookworm can remain viable while passing through the alimentary canal of chickens and can later hatch and develop in chicken feces. It was found, however, that the great majority of hookworm eggs ingested by chickens fail to produce infective larvæ. Spots of soil infestation could be established around drinking fountains by chickens which had been fed hookworm eggs day after day. Newly hatched hookworm larvæ passed through the digestive tract of the chickens alive, but infective larvæ which were fed the chickens were not found



in the feces. The author concludes that a comparison of the reduction in infective hookworm larvæ after ingestion by fowls with the danger of the establishment of infective spots by them, convinces him that chickens are more beneficial than harmful in the control of hookworm disease in Trinidad.

---

**V. The Domestic Pig and Hookworm Dissemination.**—J. E. ACKERT and FLORENCE K. PAYNE (*Am. Jour. Hyg.*, 1922, 2, 39) conclude from a series of experiments that a high percentage of the eggs of human hookworm swallowed by domestic pigs are able to produce infective larvæ, and that the free-range pig is an important factor in the dissemination of human hookworm eggs. A preliminary description is given of *Necator suillus* n. sp., which was found to be common in the domestic pigs of Trinidad, B. W. I.

---

**VI. A Study of the Effect of Hookworm Control Measures on Soil Pollution and Infestation in a Sugar Estate.**—W. W. CORT and G. C. PAYNE (*Am. Jour. Hyg.*, 1922, 2, 107) in this paper make an intensive epidemiologic study of an area in a sugar estate in Trinidad, British West Indies, to determine the exact sources of human infestation and to learn the effect on soil pollution and soil infestation of the control campaign. Of the 142 East Indians and negroes living in barracks on this area 117, were found by fecal examination to be infected with hookworms. Control measures were instituted as in the International Health Board campaigns in the West Indies including educational measures, the building of latrines and a series of three treatments. Before the introduction of the control work soil pollution was wide spread and very gross, being especially concentrated at certain easily accessible places near the edge of a cane field near the barracks where the people lived. Examinations for infective hookworm larvæ of soil samples taken from this area showed very heavy soil infestation at the places of soil pollution in the cane field, but very little pollution near the barracks or in the yards. It was found that hard packed clay-loam soil when without vegetation was not favorable for the development of hookworm larvæ. The localized character of the soil infestation, especially in the cane field, showed that there was but little active migration of the infective hookworm larvæ from their places of development, although the examinations from the drains showed that they were carried a considerable distance by water. The study of the habits of the people of this area, in relation to the distribution of soil infestation, suggested that most of their infestation must have come from the habit, which so many of them had, of visiting certain places in the cane field for the purpose of defecation. Surveys in the cane field showed a great reduction of soil pollution after the building of an adequate number of latrines and the carrying on of an educational campaign. After the reduction of soil pollution in the strip along the edge of the cane field and the treatment of the people of the area, series of samples taken at intervals showed a rapid dying out of infective hookworm larvæ from this area, so that in about six weeks soil infestation was practically eliminated.

**VII. An Epidemiologic Study of Hookworm Disease in a Cacao Estate.**—W. W. CORT and G. C. PAYNE (*Am. Jour. Hyg.*, 1922, 2, 149) find that people living in three unselected houses on a cacao estate in Trinidad, British West Indies showed a heavy infestation with hookworms. Soil pollution in this area was almost entirely restricted to definite spots—"natural latrines"—in the cacao grove near the barracks studied. The examination of soil samples for infective hookworm larvæ showed very little soil infestation anywhere in the area, except at the "natural latrines" in the cacao, and the conclusion can be drawn that almost all the human infestation must have come from the visits to the pollution spots in the cacao. Examinations of the soil of the intensely polluted spots in the cacao, six weeks after three routine treatments had been given to the people, showed a very marked reduction of soil infestation, indicating that in this situation the life of the infective hookworm larvæ is short.

---

**VIII. Experiments on the Migration of Hookworm Larvæ in Soils.**—D. L. AUGUSTINE (*Am. Jour. Hyg.*, 1922, 2, 162) shows in a series of experiments in which mature hookworm larvæ were studied in the soil, that they did not migrate actively in periods varying from fifteen hours to forty-two days. It was shown, however, that hookworm larvæ may be carried out from centers of soil infestation by surface water, and that they can establish themselves in the new locations when the water recedes. Soil scraped from the shoes of men who had passed through places of intense soil infestation was found to contain numbers of infective hookworm larvæ, suggesting another method of distribution. The conclusion is drawn that soil infestation is much more limited to the places of soil pollution than was generally supposed.

---

**IX. On the Position of the Infective Hookworm Larvæ in the Soil.**—D. L. AUGUSTINE (*Am. Jour. Hyg.*, 1922, 2, 172) found that infective hookworm larvæ under optimum conditions of moisture and temperature remain on or very near the surface of the soil. They creep up pieces of wood, decaying vegetation, and other objects, only as far as the film of moisture extends; but are not found in drops of water on the leaves of green plants. At centers of soil infestation in the field where the surface is covered with leaves or twigs, the larvæ are found on the leaves or twigs when they are moist, but as the vegetation dries the larvæ retreat to the soil below.

---

**X. Experiments on the Length of Life of Infective Hookworm Larvæ in Soils.**—D. L. AUGUSTINE (*Am. Jour. Hyg.*, 1922, 2, 177) reports a series of laboratory experiments on the length of life of mature hookworm larvæ in soils of various types (clay-loam and sand), which showed a great reduction in numbers of larvæ occurring within two or three weeks, a fairly constant small percentage of the larvæ remaining alive up to seven weeks and a complete dying out after that time. The loss of the sheath in the soil was not found to shorten the life of the mature larvæ under favorable conditions. Unsheathed larvæ were able to penetrate the skin of an experimental rat. The conclusion was drawn that environmental conditions such as tropical temperatures, which tend to increase the activity of the mature hook-

worm larvæ, will shorten their lives by the more rapid using up of the stored food material. It is evident from the experiments recorded in this paper and from the studies in the field recorded above that under tropical conditions, at least, the length of life of the mature hookworm larvæ in the soil is much less than was previously supposed.

**XI. Vertical Migration of Infective Hookworm Larvæ in the Soil. (Preliminary Report).**—FLORENCE K. PAYNE (*Am. Jour. Hyg.*, 1922, 2, 254) found that in clay-loam soil in which the distribution of moisture was uniform, buried hookworm larvæ did not migrate upward more than two inches. In saturated soil on which water was standing there was a high death rate of larvæ and little migration. In experiments with clay-loam soil in which the conditions of rising ground water were stimulated, there was a considerable migration of buried larvæ, 74.4 per cent of those recovered having migrated three inches or more, 15.4 per cent more than five inches and a few more than seven and a half inches. A distinct reduction in the stored food granules of the intestinal wall was noted in larvæ after vertical migrations of only an inch or two and almost a complete loss of these granules came about in those which had migrated five or six inches. This loss of stored granules in larvæ which had migrated different distances is clearly shown in a series of eleven photomicrographs. This series is very suggestive since it shows how quickly intense activity will reduce the food reserve in infective hookworm larvæ.

**The Prevention of Tuberculosis. Theory and Possibilities.**—LEWIS (*Am. Rev. Tuberc.*, 1922, 6, 229) states that it would seem evident that tuberculosis, whether bovine or human in type, is alike gained for the most part during early childhood; that either type may be activated and reactivated by all forms of pathogenic microorganisms; and that the balance or resistance of the infected individual is measured by the defects of the individual in their relation to air and food metabolism. Such factors have ever been submerged in the various theories of attack on prevention. Prevention has been accomplished by prevention of the activation of the tubercle bacillus by uncontaminated water and protection against filth-borne diseases like hookworm infection. The subjection of recurring cyclic frequencies of respiratory diseases, notably through the streptococcus, alike the activator and complicator of those specific diseases as well as tuberculosis, and the correction of anatomical defects of human beings are further essential factors. As evidenced by epidemiology and vital statistics, the path of the many into the one and the one into the many of Aristotle takes direct cognizance not of the tubercle bacillus only as the path, but rather as one of the many in the direct prevention of tuberculosis.

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only with the distinct understanding that they are contributed exclusively to this JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

DECEMBER, 1922

---

ORIGINAL ARTICLES.

INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER), WITH  
A REPORT OF TEN CASES.

BY WARFIELD T. LONGCOPE, M.D.,

BALTIMORE, MD.

(From the Medical Clinic Presbyterian Hospital and the Second Medical Division,  
Bellevue Hospital, New York.)

UNDER the term "akute sublymphoemische lymphomatosis," "glandular fever," "infectious mononucleosis" and "acute benign lymphoblastosis" there has been described a symptom-complex which, though not very common, is of sufficiently frequent occurrence to be of importance both from the practical and from the theoretical standpoint. The matters which are of practical importance have to deal with the diagnosis, the etiology and, should the disease prove to be an entity, with the mode of transmission and epidemiology; the matters of theoretical importance have to do with the classification of this symptom-complex and its relationship to other diseases of the lymphatic apparatus and most particularly to leukemia.

During the last few years it has happened that several acute infectious diseases which formerly were of comparatively rare occurrence and very imperfectly studied have assumed great importance by reason of the fact that they became epidemic. It is only necessary to call to mind in this connection poliomyelitis, encephalitis, influenza of course, and more recently a form of jaundice which has appeared in various parts of this country. The epidemics of these diseases serve to emphasize the fact that any acute infection is worthy of serious study and that every attempt should be made to add information about those which at the present time are imperfectly understood. It is for this reason that the following ten examples are presented of a disease or

symptom-complex which presents many perplexing features of interest.

In 1889, E. Pfeiffer<sup>1</sup> described a condition in children which he called "Drusenfieber," and which was characterized by a short febrile course accompanied by enlargement and tenderness of cervical lymph nodes. The disease occurred often in house epidemics. During the next fifteen to twenty years there were numerous references in literature to this condition of glandular fever, notably by Korsakoff,<sup>2</sup> Lublinski,<sup>3</sup> Schlissner,<sup>4</sup> Terflinger<sup>5</sup> and Jones.<sup>6</sup> In 1896, J. Park West<sup>7</sup> reported an epidemic of 96 cases from eastern Ohio. The clinical descriptions in these older papers picture with considerable detail a febrile disease lasting nine to twenty-seven days, accompanied by an enlargement of the lymph nodes, especially those of the neck, but at times of all the superficial groups as well. In some instances there was abdominal tenderness and frequently the spleen and the liver were enlarged. Mention is sometimes made of the synchronous occurrence of infections of the upper respiratory tract, but frequently it is stated specifically that there was no accompanying tonsillitis. Recovery was the rule.

Unfortunately, in none of these reports is there any mention of the leukocyte count or of the condition of the blood, and though Tidy and Morley,<sup>8</sup> who have recently reviewed the clinical aspect of this whole subject, regard the instances of glandular fever occurring in such epidemics as identical with the condition called today infectious mononucleosis, there is no proof that this identity exists.

The very unusual occurrence of a marked mononucleosis accompanying an acute infection has attracted from time to time the attention of several observers. Türck,<sup>9</sup> in 1907, recorded 3 such cases that have frequently been alluded to in literature. One case with angina and glandular enlargement resembled an acute leukemia with recovery. Marchand<sup>10</sup> recorded a similar case in 1913, and in the same year Cabot<sup>11</sup> reported 4 cases of acute local infections associated with lymphadenitis in which blood counts showed that the leukocytes varied from 9000 to 30,000 with a percentage of lymphocytes varying from 67 per cent to 82 per cent. A year later, in 1914, Hall<sup>12</sup> recorded an instance of what he believed to be acute leukemia with recovery. The disease occurred in a man, aged twenty-three years, and was characterized by fever, tonsillitis, enlargement of the lymph nodes and spleen, a leukocytosis reaching 35,000 with 89.6 per cent of mononuclear cells. There was complete and uneventful recovery. Deussing<sup>13</sup> later reported 3 cases of diphtheria-like sore throat in boys associated with a lymphocytic reaction. In these cases also there was fever associated with enlargement of the lymph nodes and spleen and a leukocytosis varying from 11,000 to 19,400 with 52 to 87 per cent of mononuclear cells. Recovery occurred in all 3 instances. During the last year, Sprunt and Evans<sup>14</sup> have reported under the term of infectious

mononucleosis 6 similar cases, all of which presented much the same clinical picture. Within the same year, Blaedorn and Houghton<sup>15</sup> have described 4 cases which they term benign lymphoblastosis. Tidy and Morley 3 cases and Morse,<sup>16</sup> under the term "glandular fever," 2 more cases. There are thus on record about 24 cases in which blood examinations have been made, though in only a few of these has any attempt been made to analyze accurately the blood picture or to investigate other important features of the disease.

It is, therefore, with an intent to add some information on these points that the following 10 cases are reported:

CASE I.—J. O. M., white, male, unmarried, aged twenty-two years. Medical student. First seen October 3, 1909. Febrile disease accompanied by enlargement of all lymph nodes, enlargement of the spleen and moderate mononucleosis. Recovery.

*Complaint.* Enlargement of lymph nodes.

*Family History.* Unimportant.

*Personal History.* Measles, scarlet fever, mumps, chickenpox as a child. Lived in North Carolina and had malaria every summer from the age of twelve to seventeen, for a period of a week or ten days with definite chills. Five years ago had pain in head with pus draining from nose and fever for one month. Last winter had "grippe" accompanied by headache and fever for four or five days. At this time leukocytes 16,000. Tonsillitis once or twice several years ago. Except for these illnesses physically strong athlete. Average weight 175 to 180 pounds.

*Present Illness.* About the middle of August, 1909, after getting water in ear from diving, noticed frontal headache, which later extended to top of head. He was slightly underweight. At this time fever every afternoon of  $101^{\circ}$  to  $102^{\circ}$ , at 3 or 4 o'clock. Three weeks after onset of fever, about September 4, all lymph nodes in body were enlarged to size of thumb nail. There was no sore throat, no digestive disturbances, diarrhea or cough. The fever persisted until September 16 and temperature has been normal since. After the middle of September, glands receded; he lost about 15 pounds in weight.

*Physical Examination.* Tall, well-built, muscular man. Throat was normal. No tenderness over frontal sinuses. All superficial lymph nodes were enlarged. Posterior cervical nodes visible and the size of beans; supraclavicular, the size of beans; axillary, the size of hazelnuts, firm, movable; epitrochlears were just palpable; the inguinal were the size of large beans. The lungs were clear. The heart was normal. The abdomen was flat; the spleen was readily palpable; the liver was not felt.

*Course of Disease.* By October 27 the patient had improved. The lymph nodes were smaller; the spleen could not be felt. On January 25, 1910, no abnormalities appeared in the physical exami-

nation. Seen again October, 1918, and found perfectly well; never had any further enlargement of lymph nodes, but two or three years ago had suffered with tuberculous pleurisy, from which he had completely recovered.

#### BLOOD COUNTS.

No.	Name.	Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono *	Lg. mono.	Bas	Myelo. n.	Unc
1	J. O. M.	Oct. 3, '09	5,800,000	85	7500							
		Oct. 3, '09	4,846,000	75	6900	46.6	6.4	36.8	10 0	0.4		
		Oct. 27, '09	...	...	7200	52.4	1.2	35.2	10 0	0.4	...	
												0.8

\* Owing to the difficulty of distinguishing many of the abnormal mononuclear cells from the small lymphocytes all of the cells have been classed together as small mononuclear cells.

*Laboratory Examinations.* During febrile period blood culture negative. Three injections of tuberculin negative. Wassermann reaction was negative.

CASE II.—P. F., male, white, unmarried, aged seventeen years. Student. Seen February 16, 1915. Subacute febrile disease with enlargement of lymph nodes and spleen, accompanied by nausea and giddiness, moderate mononucleosis. Recovery.

*Complaint.* Enlargement of lymph nodes.

*Family History.* Unimportant.

*Personal History.* Chickenpox, measles, mumps, whooping cough as a child. Jaundice at ten years of age. Mild scarlet fever at fourteen years.

*Present Illness.* On November 23, 1914, was feeling slightly under par, easily tired, had had occasional headaches with some giddiness. About December 9 he was occasionally nauseated. The temperature was 99.6°, the blood-pressure was 110/65. On December 10 he awoke with headache and chilly sensation and with a temperature of 101°. That afternoon the temperature rose to 102° and an irregular fever continued for three days, reaching normal on December 13. On December 16 the skin was clear, the lungs and heart were normal, the abdomen was soft, the spleen was felt just at the costal margin, the liver was not palpable. The cervical, axillary and inguinal lymph nodes were all palpable, the largest being the posterior auricular on the right side, which was about 1 cm. in length. These were quite soft and freely movable. The giddiness and enlargement of the lymph nodes continued.

*Physical Examination.* February 16, 1915 (summary): The patient was a nervous, overgrown, thin boy. The throat was normal. The lungs and heart were normal. The abdomen was soft. The spleen could be felt at the costal margin. The superficial lymph nodes were in the same condition as noted above. One lymph node in the left axilla was removed for microscopic examination.

*Course of the Disease.* The patient was placed on roentgen-ray treatment. From February 16 to 24 there was slight fever reaching  $100^{\circ}$  to  $101^{\circ}$  in the evening and  $99^{\circ}$  in the morning. After February 24 it became normal. The lymph nodes diminished in size. The eye-grounds were normal. On April 23, 1915, the patient was greatly improved, the lymph nodes having all disappeared. The spleen could not be felt. The patient gradually progressed to complete recovery.

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Oct. 16, '15		...	6300							
Jan. 17, '16	4,900,000	85	...	51.0	3.0	37.0	9.0			
Feb. 12, '16		...	5000	53.0		38.0	9.0			
Apr. 23, '16	...	...	5200	65.0	11.0	17.3	5.7	1.0		

*Laboratory Examinations.* On December 15 urine examination showed nothing abnormal. Sputum was negative for tubercle bacilli. No malarial parasites were found in the blood. Diazo reaction was negative. Later repeated examinations of the urine and sputum showed nothing abnormal. Roentgen ray on December 10 showed lungs clear, some increase in oval root shadow suggesting lymph node. The Widal reaction was negative. Microscopic examination of the lymph node excised was as follows: "This on section shows almost complete loss of the normal structure. There is marked lymphoid hyperplasia, while the germinal centers show karyorrhxic and karyokinetic nuclei. In the lymph spaces between the cords there is active proliferation of the epithelioid cells of the reticulum with formation occasionally of large uninuclear cells almost of giant size. A few of these large epithelioid cells are also mixed in with the cells in the lymph cords. Occasionally an eosinophilic leukocyte is seen. Picture suggests very strongly Hodgkin's disease, though one would scarcely dare to make a definite positive diagnosis. It seems advisable, however, to treat the case as such."

CASE III. G. E. (No. 15721), white woman, widow, aged thirty years, housewife. Admitted to the Presbyterian Hospital, July 29, 1915; discharged November 1, 1915. Acute febrile disease of forty-four days' duration, chills, sore throat, enlarged lymph nodes and spleen, moderate mononucleosis. Recovery.

*Complaint.* Headaches and fever of five days' duration.

*Family History.* Unimportant.

*Personal History.* Works as typist. Husband died two years ago. She was married at nineteen and had one child living and



well; there were no miscarriages. She had had measles and pertussis in early childhood; scarlet fever at twelve years. Two years ago she had had an operation on the nose for deafness in the right ear. There was no history of rheumatic fever, pneumonia or typhoid fever.

*Present Illness.* Five days ago she developed sore throat with cough and pain on swallowing. That evening she had a sudden chill followed by high fever. The fever continued. Headaches and stiffness in the back developed; she had eructations and vomited on the morning of admission. She had continued at work until the day of admission.

*Physical Examination.* Well-nourished, acutely ill young woman. There was no dyspnea. Over the chest and abdomen were scattered pink papules and a few macules resembling rose spots. The patient was very deaf. The tongue was dry. There were several decayed teeth and moderate pyorrhea. The pharynx was very red; the thyroid gland was palpable. The lungs were clear. The heart was normal except for an occasional premature contraction. The pulse was 100. The blood-pressure was 126/72. The abdomen was full; the liver was not palpable. The spleen was just palpable. The extremities were normal. The temperature was 105.3°. Typhoid fever was suspected as a provisional diagnosis.

*Course of the Disease.* For two weeks after admission the temperature remained constantly between 101° and 103°. The lungs remained clear. The spleen increased slightly in size. No further eruption suggestive of rose spots appeared. There was only moderate prostration. On August 14, 1915, a small lymph node was noticed behind and anteriorly to each ear and a swollen tender node was found on the right side of the neck. On August 15 there was general enlargement of the lymph nodes of both posterior and anterior triangles, the largest being the size of a hickory nut beneath the angle of the right jaw. They were all discrete, firm, movable, somewhat tender. The epitrochlears were not felt. On August 18 the fundi were normal. The left ear drum was normal. The right ear drum was sclerosed and retracted. On August 23 a lymph node was removed for microscopic examination. By August 27 the nodes had somewhat diminished in size. The temperature was lower and did not rise above 100°. By September 4 the spleen was slightly enlarged and hard. The lymph nodes had practically disappeared except one in the right cervical region, which remained enlarged and firm. The patient rapidly improved and went on to complete recovery. The pulse varied during the course of the disease between 70 and 100.

An examination of the mononuclear cells in the blood on September 10 showed that they did not give an oxidase reaction. No malaria organisms were found (Fig. 1).

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
July 30, '15	...	85	3,400	56.0	1.0	41.0	2.0			
July 31, '15	...	...	3,400	60.0	..	38.0	2.0			
Aug. 3, '15	...	...	5,400	54.0	...	43.0	3.0			
Aug. 9, '15	...	...	9,800	44.0	...	56.0				
Aug. 15, '15	5,616,000	81	8,800	28.0	1.0	71.0				
Aug. 25, '15	...	...	7,800	28.0	4.0	68.0				
Sept. 10, '15	...	...	7,600	35.0	1.0	63.0	1.0			
Nov. 1, '15	...	...	11,100	37.0	...	61.0	2.0			

*Laboratory Examinations.* On July 31 blood culture gave no growth. The Wassermann reaction was negative and the Widal reaction was negative. On August 7 the Widal reaction was again negative. The blood culture showed contaminating growth of bacteria. On August 8 bacterial examination of stool showed no

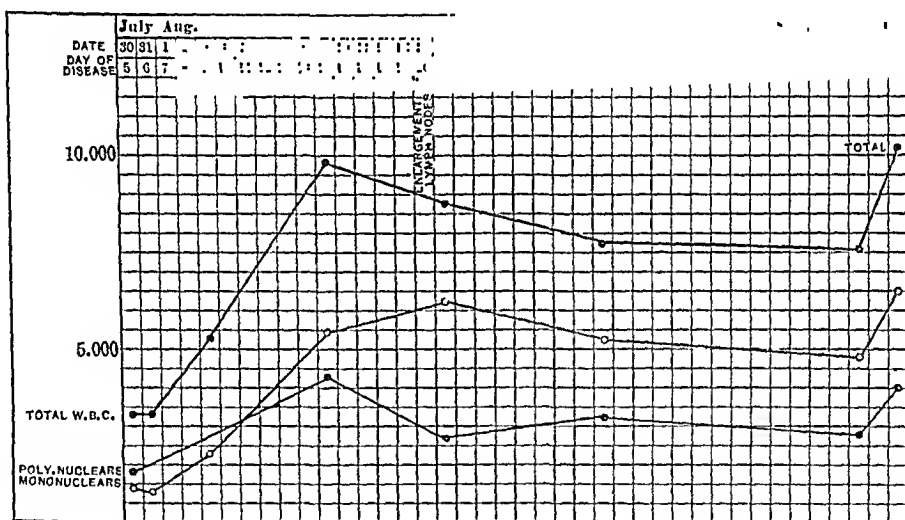


FIG. 1.—Case III. Chart showing changes in total number of white blood cells (upper line). Absolute number of mononuclear cells (°———°) and absolute number of granular cells (°———°).

typhoid bacilli. On August 9 cultures of urine were sterile. On August 20 blood culture was sterile, Widal reaction negative. On August 27 cultures from urine showed no typhoid bacilli. On August 29 cultures from stool showed no typhoid bacilli. On September 10 von Pirquet reaction was negative. The urine was usually acid, varied from 1014 to 1024, contained constantly a faint trace of albumin; the sediment showed epithelial cells and leukocytes.

CASE IV.—E. S., white, male, unmarried, aged twenty-one years, medical student. Admitted to the Presbyterian Hospital, April 14, 1916; discharged April 24, 1916. Acute febrile disease, ushered

in by acute tonsillitis, followed by chilly sensations, fever, profuse perspiration, marked enlargement of lymph nodes and spleen and marked mononucleosis. Recovery.

*Complaint.* Sore throat, one week's duration.

*Family History.* Unimportant.

*Personal History.* Measles as child; no scarlet fever nor diphtheria. Had been subject to sore throat (once a year) and had had one bad attack of tonsillitis. Stated that tonsils had been removed at age of nine or ten. Denied venereal infection. Had had anti-typhoid inoculations two years previously. Had usually had excellent health. Best weight, 150 pounds.

*Present Illness.* Two weeks before admission he had a cold in his head but was not ill; he suffered no constitutional disturbances. Seven days before admission had had severe headache and sore throat with chilly sensations next day and fever varying from normal to  $102^{\circ}$ . Had been at work; felt very badly; had had profuse perspiration. Appetite was poor. There was no nausea, vomiting, diarrhea nor cough.

*Physical Examination.* Well-developed young man, acutely ill. Right tonsil was largely absent; left tonsil was regular, swollen, very large, red and showed exudates in the crypts. The entire pharynx was red and the lymphoid tissue was swollen. The lungs and heart were normal. The pulse was 100; the blood-pressure was 124/60. The abdomen was full, the spleen was readily palpable 2 cm. below the costal margin, and the liver edge was palpable at the costal margin. The lymph nodes were all much enlarged and tender. The submental and cervical lymph nodes were the largest and were firm and movable. The posterior cervical, axillary, supraclavicular and inguinal nodes were all moderately enlarged and firm.

*Course of the Disease.* On April 17 the spleen reached 4.5 cm. below the costal margin. The lymph nodes were somewhat smaller. The throat was still much swollen and red. The disk of the right fundus was normal. The disk in the left fundus showed a hazy margin. On April 20 the lymph nodes remained about the same; the spleen was somewhat smaller but it was palpable below the costal margin. On April 24 the throat was still swollen and the cervical lymph nodes were large. The spleen was still palpable. The temperature varied between  $100^{\circ}$  and  $102.5^{\circ}$ , falling to normal on April 21. The pulse ranged between 80 and 100. The patient rapidly improved and went on to complete recovery. On November 23, 1916, he was in splendid condition; the tonsils had been completely removed. The cervical lymph nodes were just palpable. The axillary, inguinal and femoral nodes were the size of dried beans. The epitrochlears were just palpable. Both the liver and the spleen could just be felt. On October 28, 1919, the patient had remained in perfect health and for months neither the spleen nor lymph nodes had been palpable.

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. cos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Apr. 14, '16	...	85	8,800	30.0	...	30.0				
Apr. 15, '16	3,800,000	84	11,200	18.0	...	82.0				
Apr. 16, '16	...	...	14,800	8.0	...	92.0				
Apr. 17, '16	...	...	18,000	6.0	...	94.0				
Apr. 18, '16	...	...	23,000	5.0	...	95.0				
Apr. 19, '16	...	...	25,200	6.0	...	94.0				
Apr. 20, '16	...	...	24,400	10.0	...	90.0				
Apr. 21, '16	5,200,000	...	20,200	8.0	...	92.0				
Apr. 22, '16	5,400,000	...	19,200	9.0	...	91.0				
Apr. 23, '16	...	...	18,000	12.0	...	88.0				
Apr. 24, '16	...	...	17,500	...	...	...				
Nov. 26, '16	5,000,000	...	7,500	70.0	...	26.0				
Oct. 27, '19	...	...	...	70.0	1.0	28.0	1.0	...	...	4.0

A large proportion of the mononuclear cells were somewhat larger than the small lymphocytes; they possessed round, oval or lobulated nuclei, surrounded by a varying rim of basophilic protoplasm which did not contain granules. There were also cells typical of the normal small lymphocyte and a few cells could not be differentiated from large mononuclear cells. Stains for oxidase granules on April 20 showed only 1 to 2 per cent of the cells which possessed these granules (Fig. 2).

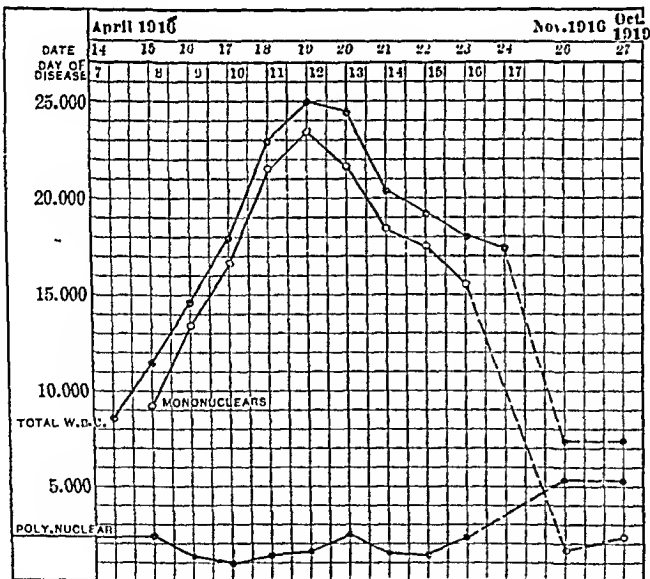


Fig. 2.—Case IV. Chart showing changes in total number of white blood cells (upper line) and in absolute number of mononuclear cells (°————°) and of granular cells (lower line —————).

*Laboratory Examinations.* On April 15 blood culture showed no growth; throat culture showed no diphtheria bacilli; staphylococci predominated in culture. On April 16 the Widal reaction was

negative. April 17 the blood culture showed again no growth. On April 18 smears from the tonsils showed the predominating organisms to be lanceolate diplococci. There were also fusiform bacilli, spiral organisms and a few large Gram-positive diplococci. April 21, blood culture showed no growth. Throat culture showed *Staphylococcus aureus* and nonhemolytic streptococci.

CASE V.—T. P., white, male, unmarried, aged twenty-one years, student. Admitted to the Presbyterian Hospital, January 22, 1917; discharged, February 7, 1917. Acute febrile disease with enlargement of the lymph nodes and spleen; moderate mononucleosis. Recovery.

*Complaint.* Fever and malaise.

*Family History.* Unimportant.

*Personal History.* Measles, croup and scarlet fever as a child. Tonsillitis in summer and fall of 1910; tonsillectomy September, 1910. Occasional attacks of appendicitis with appendectomy in March, 1914. Colds in head during November, 1916. Denies venereal infection. Best weight, 145 pounds.

*Present Illness.* Gradual onset over a period of a week with continuous headaches, evening temperature reaching  $101.8^{\circ}$  at times; there was pain in the eyes, occasional slight cough without expectoration and general malaise, anorexia, and constipation. With the onset of fever the patient noticed enlargement of lymph nodes in the cervical and inguinal regions which had never occurred before.

*Physical Examination.* Well-built young man not very ill. The tonsils were absent. There was enlargement of the lymphoid tissue on the posterior pharyngeal wall. The lungs and heart were normal. The abdomen was soft, not tender; the edge of the spleen was easily felt; the liver was not palpable. The superficial lymph nodes were practically all enlarged. The posterior cervical nodes on both sides were quite large; the anterior cervical nodes were not so large except for one solitary submental node on the right side about the size of a lima bean. The supraclavicular nodes on the right side were slightly enlarged. The axillary and inguinal nodes were enlarged. The epitrochlears were not felt. All the nodes varied from the size of a pea to that of a lima bean, were discrete, firm, movable and not tender.

*Course of the Disease.* From January 22 to the 31st there was slight fever varying from  $99.2^{\circ}$  to  $100.3^{\circ}$  with one rise to  $102.3^{\circ}$ . On January 26 the fundi were normal, the posterior cervical lymph nodes were somewhat larger and tender on pressure, firm, isolated, freely movable; the submental and axillary nodes were unchanged; the inguinal and femoral nodes had increased slightly in size; the tip of the spleen was just palpable. By February 7 all the lymph nodes had diminished in size and the spleen was no longer palpable.

There was uncomplicated convalescence and recovery. On October 26, 1919, the patient was well. He had been in France on active service, had been gassed and had had influenza. At this time there was no enlargement of the lymph nodes; the spleen was not palpable. The heart and lungs were normal.

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Jan. 22, '17	...	...	10,700	25.0	1.0	67.0	6.0	1.0		
Jan. 23, '17	...	...	...	20.0	...	72.0	1.5	3.5	1.5	
Jan. 24, '17	...	...	9,700	27.5	0.5	56.5	5.0	1.0	1.0	8.5
Jan. 26, '17	4,530,000	90	...	...	...	...	...	...	...	...
Jan. 29, '17	...	...	8,250	43.0	...	52.0	5.0	...	...	...
Feb. 7, '17	...	...	8,750	42.0	3.0	47.5	5.0	...	1.0	...

A large proportion of the mononuclear cells were abnormal in appearance, being larger than the small mononuclear lymphocytes, showing a round, oval or lobulated nucleus; a few cells contained nucleoli. The protoplasm varied in width; usually took a basophilic stain and showed no granules. There were also cells indistinguishable from the normal small lymphocyte and from the large mononuclear cells. On January 24, 56 per cent of these mononuclears did not contain oxidase granules; 36 per cent of the polymorphonuclear cells did contain oxidase granules.

*Laboratory Examinations.* January 23, blood culture gave no growth of bacteria. The Wassermann reaction was negative in both antigens. The Widal reaction was negative. The urine culture showed no growth. Complement-fixation test for tubercle bacilli was negative. January 24, roentgen-rays of the lungs showed nothing abnormal. January 26 and 27, sputum showed no tubercle bacilli. January 30, von Pirquet reaction was questionably positive in seventy-two hours. Urine showed specific gravity 1020, acid, amber, no albumin nor glucose, no casts.

CASE VI.—A. B., colored boy. Admitted to the Presbyterian Hospital, February 6, 1917; discharged, February 23, 1917. Acute febrile disease with enlargement of lymph nodes, spleen and liver, and marked mononucleosis. Recovery.

*Complaint.* Cough, enlarged glands and night sweats of one month's duration.

*Family History.* Mother is said to have tumor of abdomen; otherwise unimportant.

*Personal History.* At the age of three years measles complicated with pneumonia. Had had attacks of tonsillitis and frequent colds. Tonsils and adenoids removed three months ago.

*Present Illness.* Cough for one month with enlargement of lymph nodes, night sweats and loss of weight amounting to 11 pounds in the last month.

*Physical Examination.* Well-developed colored boy. The tonsils were absent. The mucous membrane of the mouth and throat was very red. There were several decayed teeth. The lungs were normal. The heart was normal in size and position. There was a systolic murmur at the apex not transmitted. The abdomen was soft, not tender. Both the liver and spleen were palpable.

*Courses of the Disease.* Until February 16 the pulse, respiration and temperature were normal. On February 16 the temperature rose to 101° and the lymph nodes increased in size and became tender. The pharynx was red and swollen. The patient progressed to convalescence. On February 23 he developed chickenpox and was removed to another hospital. Later the carious teeth were removed and the remaining lymphoid tissue resected from the pharynx. On October 18, 1919, he was again admitted to the hospital, where he suffered an attack of typhoid fever, at which time typhoid bacilli were grown from blood culture. There was no pathologic enlargement of the lymph nodes at this time.

#### BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Feb. 7, '17	...	...	20,600							
Feb. 8, '17	...	...	26,200	60.0		30.0	10.0			
Feb. 12, '17	...	...	14,100	41.0	4.0	50.0	4.0	1.0		

October 21, 1919, the coagulation time of the blood was twelve and a half minutes; the control was three minutes. The bleeding time was two minutes ten seconds; the control was one minute and five seconds.

*Laboratory Examinations.* On February 7, 1917, von Pirquet was negative. Roentgenogram of the lungs showed nothing abnormal. Cultures from the throat showed no diphtheria bacilli. On February 15 the Wassermann reaction was negative in both antigens. The urine showed a specific gravity of 1020, acid, no albumin nor glucose, no casts.

CASE VII.—S. M., white youth, aged thirteen years, choir boy. Admitted to the Presbyterian Hospital, June 13, 1917; discharged, June 18, 1917. Acute febrile disease, enlargement of lymph nodes and spleen, well-marked lymphocytosis. Recovery.

*Complaint.* Enlarged glands in neck of two weeks' duration.

*Family History.* Unimportant, except that his mother three years ago had had angioneurotic edema lasting one year.

*Previous History.* Measles and mumps on the right side, pertussis, chickenpox. He had been subject to colds and described two abscesses in the ears. A few years ago adenoids and tonsils were removed on account of occasional sore throat. No scarlet fever nor diphtheria. Best weight, 105 pounds. No previous glandular enlargement noted. On November 14, 1913, he had been examined at school and found normal.

*Present Illness.* Two weeks before admission he had accidentally noticed some glands in the neck. At the same time he had a slight fever reaching  $101^{\circ}$  at night and  $99^{\circ}$  in the morning, lasting from June 1 to June 11. On June 7 the temperature was  $101.8^{\circ}$ . On June 10 and 11 his physician had made leukocyte counts which are recorded below.

*Physical Examination.* On admission (summary): Temperature normal; pulse 60. The patient was a well-developed boy. The color was good. There were no eruptions. The throat showed nothing except some lymphoid tissue which remained in the right tonsillar fossa. The lymph nodes beneath the upper part of the sternomastoid on both sides of the neck were enlarged and readily palpable. There were also many shotty lymph nodes in the anterior and posterior triangles of the neck on both sides. The axillary, epitrochlear and inguinal lymph nodes were palpable but not definitely enlarged. The lungs were normal. The heart was of normal size; there was a loud systolic murmur at the apex with a marked sinus arrhythmia. The abdomen was soft; the spleen was easily felt 2 cm. below the costal margin. The reflexes were normal.

*Course of the Disease.* The temperature remained normal. By June 16 the patient was up and about the ward. The lymph nodes were definitely diminished in size but were still large, though not tender. By June 18 the spleen was smaller and the patient felt perfectly well. The enlargement of the cervical lymph nodes had decreased somewhat. Two oblong glands at the angle of the jaw were the largest. They were about 2 cm. long and 1 cm. wide, firm, movable but not tender. He left the hospital on June 18. On July 20 he was seen by Dr. Neergaard, who noted that all the lymph nodes in the neck were still palpable. On October 3, 1919, the patient had grown considerably and looked and seemed very well. All the superficial lymph nodes were still palpable. The spleen could not be felt.

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
June 10, '17	...	S5	16,000							
June 11, '17	...	S5	15,266	10.0	1.0	76.0	13.0			
June 14, '17	5,200,000	S5	9,200	3.0	...	90.0	6.0	...	1.0	
June 16, '17	...	...	8,600	13.5	...	73.0	13.5			
Oct. 3, '19	5,304,000	99	9,000	49.0	...	37.0	14.0			



June 14, 1917, blood group I, mononuclear cells (Hastings's stain) appeared from one-fourth to one-half as large again as the red blood cells, with large deeply staining nuclei; most of the cells have a narrow rim of basophilic cytoplasm without granules. Examination of the smear made on June 15 showed the following appearance: Mononuclear cells were of two or possibly three varieties:

I. Cells which could not be differentiated from the normal small lymphocytes of the blood.

II. Cells larger in size than the small lymphocyte with oval, kidney-shaped or slightly lobulated nucleus staining fairly deeply in Wright's stain, without definite nucleoli, usually eccentrically placed and surrounded by a fair amount of basophilic protoplasm of a general ground-glass appearance. The protoplasm of these cells did not contain definite granules.

III. Cells larger than type II and indistinguishable from the normal large mononuclear cells. Cells of type II predominated.

June 14, cells of type II were still predominating.

June 16, cells of type II were much less numerous, cells of type I predominating. None of the mononuclear cells contained oxidase granules.

Röntgen-ray of the lungs showed nothing abnormal. Urine varied in specific gravity from 1025 to 1030, acid, amber, and on one occasion showed a faint trace of albumin; no glucose; occasional leukocytes were found. The tuberculin reaction was negative.

CASE VIII.—F. de A. (No. 34874), Italian girl, unmarried, aged twelve years, school. Admitted to the Presbyterian Hospital, December 13, 1920; discharged, January 6, 1921. Febrile disease with moderate fever, accompanied by slight enlargement of the lymph nodes, moderate lymphocytosis, cardiac arrhythmia with premature contractions, abdominal pain, vomiting and constipation. Recovery.

*Complaint.* Pain in right side of abdomen of five days' duration.

*Family History.* Unimportant.

*Previous History.* She had had pneumonia, measles and an attack of diarrhea in infancy and had had frequent attacks of tonsillitis accompanied by fever and often by nausea, vomiting and constipation. During the summer of 1920 she had pain in the right shoulder for about one month without fever. No other evidence of rheumatic fever. No scarlet fever or diphtheria. Menses began at eleven years and six months, regular and profuse.

*Present Illness.* November 24, 1920; tonsillectomy was performed. Since then she had had intermittent fever with considerable malaise, constipation and vomiting at times. Five days ago she began to have abdominal pains, at times confined to the right side. Usually the pain was dull but during the last few days it had

been cramplike, coming on about every three hours accompanied by vomiting. Five days ago small pink spots appeared over entire body and extremities gradually increasing to large swollen areas, which disappeared.

*Physical Examination.* (Summary.) The patient was a well-nourished white girl, rather overdeveloped for her age. There was considerable pigmentation about the eyes. The lips and mucous membranes were slightly pale; there was no icterus. Over the abdomen there was a macular eruption of irregular, small, dull red spots. This did not itch. The tonsillar pillars and fossæ were slightly hyperemic. The submaxillary lymph nodes were definitely enlarged, firm but not tender. The posterior cervical lymph nodes were small but tender. The axillary and inguinal lymph nodes were moderately enlarged but not tender. The lungs were clear. The heart was not enlarged. The pulse was 78. There was a soft blowing systolic murmur heard best at the apex; some accentuation of the second pulmonic sound; occasional premature contractions. The abdomen was soft. There was tenderness in the right lower quadrant. There was some voluntary spasm of the muscles. The liver and spleen were not palpable.

*Course of the Disease.* From the day of admission to December 31 the patient had an irregular fever varying from  $97.8^{\circ}$  to  $101^{\circ}$  and  $102^{\circ}$ . The pulse varied from 78 to 110. On December 17 the premature contractions persisted. On December 21, though she had been running a constant low fever, she felt perfectly well. There was no cough. The abdominal pain had disappeared and there were no night sweats. The lymph nodes remained persistently large and tender. By January 13 she had been well enough to go to school for several days. The posterior cervical lymph nodes were the size of beans, the submaxillary, anterior cervical and supraclavicular were the size of peas to beans; the axillary and epitrochlears were not definitely palpable. The inguinal and femoral nodes were just palpable. There was a loud systolic murmur at the pulmonic area. The spleen and liver were not palpable. On February 3 the lymph nodes were smaller but all were still palpable. By April 17 all the superficial lymph nodes could be felt but with difficulty.

## BLOOD EXAMINATIONS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
Dec. 16, '20	7,140,000	80	12,800	38.0	1.0	15.0	45.0			
Dec. 29, '20	3,800,000	68	12,900	21.0	4.0	60.0	15.0			
Jan. 13, '21	...	...	13,300	45.4	2.0	44.4	5.0	...	0.4	2.8
Jan. 21, '21	4,884,000	79	11,760	60.0	2.0	37.0	1.0			
Apr. 7, '21	...	...	9,200	65.7	2.0	23.0	7.7	...	...	1.6

The mononuclear cells were somewhat larger than the small lymphocytes and contained a round, oval or lobulated nucleus surrounded by a rather narrow zone of protoplasm which was basophilic. This type of cell predominated among the mononuclears.

*Laboratory Examinations.* December 13, 1920: An electrocardiogram showed rate of 125. *A-V* interval, 0.14 to 0.16. Ventricular premature contractions. T inverted. Blood culture gave no growth. Wassermann reaction was negative with both alcoholic and cholesterin antigens. The Widal reaction was negative. December 16, stool was soft, brown, guaiac reaction was negative for occult blood. December 22, blood culture again showed no growth of bacteria. December 31, roentgen-ray of the lungs showed slight accentuation of the linear markings of the right lung.

CASE IX.—E. C. (No. 50373), white, male, unmarried, aged twenty-eight years, physician. Admitted to the Presbyterian Hospital, May 27, 1919; discharged June 17, 1919. Acute febrile disease associated with chills, sweating, severe pharyngitis, enlargement of lymph nodes and spleen, marked lymphocytosis.

*Complaint.* General malaise for seven days, intermittent chills and fever.

*Family History.* Unimportant.

*Previous History.* The patient had always been healthy. He had had an appendectomy and two years ago tonsillectomy performed. In January, 1920, he had a suppurating abscess of the left tonsillar fossa from which creamy pus was evacuated.

*Present Illness.* The patient was perfectly well until a week ago, when he felt so chilly that he wore his overcoat. His temperature ranged between 99° and 100°. The next day there were vague aching sensations; the throat was red and sore. That evening the temperature was 101°. During the night he had a drenching sweat. He continued to feel badly. He had frequent chills lasting about one and a half minutes followed by fever of 102°, severe headache and drenching night sweats. He had had anorexia and irregular severe frontal and occipital headache. Since May 27 there had been no further chills. The eyeballs had been tender. The throat had been increasingly sore and he had had a little cough, with no sputum, epistaxis, no hemoptysis, no pain in the chest.

*Physical Examination.* The patient was a well-nourished well-developed man, with a flushed and feverish appearance, looking acutely ill, sweating slightly. The temperature was 100.4°; the pulse was 100. The conjunctivæ were deeply injected. Ear drums showed some redness. Buccal mucous membrane showed fine petechiæ along the line of closure of the teeth. The tonsils were not seen. The pharynx and soft palate were bright red and showed patches of dirty yellow exudate scattered over them. There was a

sharply raised red edge on the soft palate. A surgical scar on the left side of the neck was visible. The lungs were normal. The heart was normal in size and there were no murmurs. The pulse was regular, the rate was 96. The blood-pressure was 115/74. The abdomen was not tender. The liver dulness came to the costal margin. The liver was not palpable. The spleen was easily palpable, soft, slightly tender, descending 6 cm. below the costal margin. The reflexes were normal. The lymph nodes were definitely and generally enlarged. The left submaxillary nodes were large and tender. The posterior and anterior cervical group, particularly on the left, were definitely enlarged and tender. There was less enlargement on the right. The epitrochlears were enlarged and the left was  $\frac{1}{2}$  cm. in diameter. One left axillary lymph node was 1 cm. in diameter. The inguinal nodes were not enlarged.

*Course of the Disease.* The condition remained about the same until June 2, with persistence of marked swelling, reddening and enlargement of the lymphoid tissue of the pharynx over which the exudate remained, and of the enlargement of the lymph nodes, irregular fever and drenching sweats. The voice became quite nasal. On June 2 he was better, fauces were less swollen, redness was disappearing, the lymph nodes showed decrease in size, tenderness of the spleen disappeared with diminution of size so that it was just palpable at the costal margin. By June 5 the temperature was normal. The throat had improved greatly. The lymph nodes were still palpable. The spleen could be felt 4 cm. below the costal margin. On discharge he looked and seemed well except for slight redness of the throat. The lymph nodes had diminished greatly in size, a few the size of peas were felt in the posterior cervical region. The left axillary and epitrochlears were just palpable. None were tender. The spleen could be felt only with difficulty. By July 26, 1921, the lymph nodes were no longer palpable except for a few in the axilla. The spleen could not be felt. Recovery was complete.

## BLOOD COUNTS.

Date.	R.b.c.	Hb.	W.b.c.	Poly. n.	Poly. eos.	Sm. mono.	Lg. mono.	Bas.	Myelo.	Uncl.
May 23, '21	6,914,000	130	7,500	56.0	...	68.0	6.0	1.0		
May 27, '21			10,700	25.0						
May 28, '21			10,200	33.0						
May 29, '21			13,000	24.0						
May 30, '21	6,848,000	120	15,400	24.0	1.0	76.0	4.0	2.0		
May 31, '21			13,320	21.0		79.0				
June 2, '21			15,400	20.0		80.0				
June 3, '21			15,800	19.0		81.0				
June 4, '21			12,600	26.0		70.0				
June 6, '21			14,700	35.0		63.0				
June 7, '21			15,200	21.0		76.0				
June 8, '21			14,600	29.0		71.0				
June 13, '21			11,900	30.0		66.0				
June 18, '21			10,600	32.0		68.0				
July 26, '21			5,920	54.0		42.0	4.0			

On May 27 the leukocytes were moderately increased. The predominating cell was a moderate size mononuclear cell with a clear robin blue cytoplasm containing in many cases a few azura-phil granules. The nuclei were round or oval. In addition there were considerable numbers of abnormal mononuclear cells somewhat larger than the normal lymphocyte and showing a more deeply staining basophilic cytoplasm, occasionally containing vacuoles. The nuclei of these cells were of the Rieder type. On May 28 there were considerable numbers of broken cells and "basket cells" in the smears. On May 29 an oxidase stain showed that the mononuclear elements of the blood did not contain oxidase granules. The abnormal mononuclears, which varied considerably in size, were more numerous than on the previous examinations.

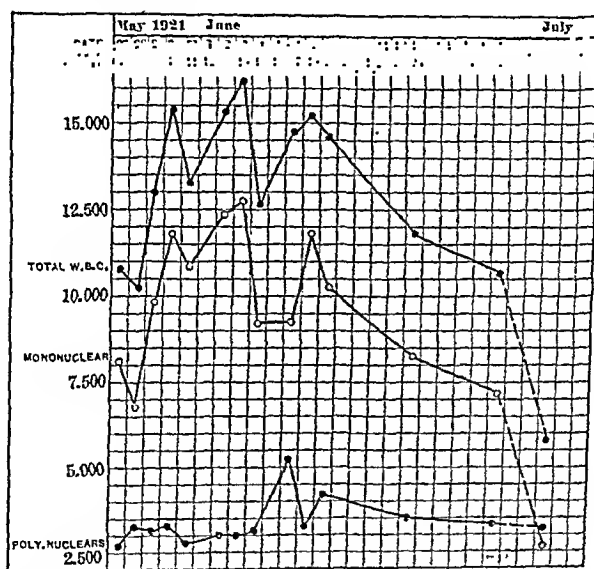


FIG. 3.—Case IX. Chart showing changes in total number of white blood cells (upper line). Absolute number of mononuclear cells (°—°—°) and of granular cells (lower line ———).

*Laboratory Examinations.* On May 27 the blood culture gave no growth of bacteria. The Wassermann reaction was negative to both antigens. The Widal reaction was positive up to 1 to 40 and 1 to 80. On May 28, roentgen-rays of the lungs showed nothing abnormal. On May 30 smears from exudate and throat showed a few Gram-negative spirilla and many varieties of cocci and bacilli, none of which seemed to predominate. Blood agar plates were streaked and culture gave *Streptococcus viridans* and *Micrococcus catarrhalis*. On June 3 smears from the throat showed numerous cocci and bacilli, fusiform bacilli and spirilla of Vincent. Aërobic cultures showed no growth for pathogenic organisms. The urine

examinations showed specific gravity varying from 1018 to 1030, acid in reaction, amber. On May 24 a very faint trace of albumin, none afterward, no glucose. Microscopically there were no casts.

CASE X.—P. A., white youth, aged fifteen years, school-boy. Admitted to the Bellevue Hospital, March 6, 1922; discharged, March 23, 1922. Acute febrile disease, associated with tonsillitis, general enlargement of lymph nodes, marked mononucleosis. Recovery.

*Complaint.* Sore throat and swelling of right side of neck.

*Family History.* One sister has rheumatism and heart trouble, otherwise unimportant.

*Personal History.* Measles and whooping cough at two years, chickenpox at five years. Five or six years ago noticed swelling of glands in the neck and beneath the jaw during colds. Had had occasional sore throats which were not severe. Last year he had trouble with his ears and the right drum was incised.

*Present Illness.* Ten days to two weeks ago he had a cold in his head, earache on the right side and a spontaneous discharge from the right ear which he thought had been present for a week before admission. Four days before admission the right side of the neck began to swell, fever increased. There was no pain except when he touched the swellings. The left side of neck also became slightly swollen, but he paid no attention to it because this occurred every winter when he had colds.

*Physical Examination.* Adolescent boy, did not appear very ill, rather thin, somewhat pale, temperature on admission, 102.8°. There was no discharge from the right ear. The pharynx was deeply congested, the tonsils enlarged and red; there was no exudate. The lungs and heart were normal. The pulse was 110. The abdomen was soft; the liver and spleen were not palpable. Practically all the superficial lymph nodes were enlarged. Those in the posterior cervical triangle were largest, the one on the right side being visible, the size of an egg; the posterior cervical nodes and those in the anterior triangle were smaller. The right axillary nodes were much enlarged; the inguinal and femoral were the size of almonds. The right epitrochlear was the size of a bean.

*Course of the Disease.* On March 7 the tonsils increased in size and pus could be expressed from them. The temperature varied between 101° and 104° until March 17; the pulse between 120 and 128; the respirations between 24 and 26. The boy seemed acutely ill and rather severely prostrated. On March 16 the tonsils were still much enlarged, red and edematous. The lymph nodes, many of which were visible in the neck, averaged from 2 to 3 cm. in length to the size of a pea. The spleen and liver could not be felt. On March 17 the temperature ranged between 99.6° and 101°, and on March 18 the temperature was normal and from that time there

was uncomplicated convalescence. On March 22 the tonsils had diminished in size, they were still large and irregular, were only slightly red and the edema had disappeared. The lymph nodes in the posterior triangle of the neck were still visible, 1 to 2 cm. in length; the inguinal and femorals were 1 to 2 cm. The spleen and liver were not palpable.

## BLOOD COUNTS.

No.	Name.	Date.	R.b.c.	Hb.	W.b.c.	Poly. n., per cent.	Poly. eos.	Sm. mono., per cent.	Lg. mono., per cent.
X	P. A.	Mar. 8, '22	...	...	15,400	16	...	84.0	
X	"	Mar. 10, '22	...	...	...	20	...	76.0	
X	"	Mar. 16, '22	...	...	16,800	27	...	71.4	1.6
X	"	Mar. 22, '22	...	...	8,000	33	...	53.0	14.0

Smears stained with Hastings's stain showed predominating mononuclear cells, which were somewhat larger than the normal lymphocyte, round or oval, had a rather deeply staining round, oval or lobulated nucleus without nucleoli. Protoplasm varied slightly in amount, took a moderately deep basophilic stain and had a ground-glass appearance, but showed no granules. There were moderate numbers of cells which were indistinguishable from the small lymphocyte and a very few mononuclear cells that were identical with the large mononuclear cells in normal blood.

*Laboratory Examinations.* Blood culture showed no growth. March 10 and 22 throat culture showed no diphtheria bacilli, but *Staphylococcus albus*, and in the smears Vincent's spirillae were observed. On March 15 smears from the throat showed spirillae and fusiform bacilli. Cultures gave streptococcus in long chains.

An analysis of these 10 cases shows that the disease occurred twice in females and eight times in males. All of the patients were under thirty years of age. Two of them were medical students and one was a doctor. The onset was, as a rule, somewhat gradual. Headache occurred in 3 cases, fever in 9, sore throat and chills in 5, cough in 3, malaise in 3, sweating in 3 and abdominal pain and vomiting in 2. During the onset enlarged nodes were observed only four times by the patients; in 1 case enlargement of the cervical lymph nodes was the first symptom noted. The disease had usually existed for at least a week before the patient was first examined. Most of the patients appeared to be very uncomfortable when they were first seen and complained particularly of the moderate fever and sweats and soreness of the pharynx or tonsillitis. In 1 case the onset was preceded by an acute otitis media. In 3 cases the tonsils were swollen, red and acutely inflamed. In 2 other cases in which the tonsils had been previously removed the lymphoid tissue

of the pharynx was swollen and the pharynx was red. In 1 case the pharynx alone was red and in one instance the disease came on after tonsillectomy. In the 2 women a faint red macular rash was observed over the abdomen on the first examination.

In all but 1 case a striking feature of the first examination was the noticeable enlargement of the superficial lymph nodes. In this 1 case the cervical lymph-node enlargement did not appear until the second week of fever. In all instances eventually the cervical lymph nodes were enlarged, felt rather firm and were tender to touch. They varied from the size of beans to a hickory nut and in most cases averaged about 1 cm. in diameter. The submental nodes were usually the largest, but both anterior and posterior cervical chains were involved. In 3 cases the enlargement extended to all the superficial nodes except the epitrochlears, and in 5 cases all the nodes, including the epitrochlears, were involved. In a few instances the enlargement was very marked and in 1 case the epitrochlears measured 1.5 cm. in length.

During the increment of the lymph nodes the fever continued and in most cases it reached for a few days  $101^{\circ}$  to  $103^{\circ}$ , being irregular and of intermittent type with diurnal rise and fall. The fever lasted from three days to about three weeks, but continued approximately for from two to three weeks in 7 of the cases.

During the course of the disease in 8 of the 10 cases the spleen became palpable and sometimes tender. The liver was palpable in one instance. Sweating was common and was in a few cases a disagreeable feature. The pulse varied from 80 to 100. In one girl of twelve years frequent premature ventricular contractions were observed during the illness. In one instance there were nausea and vomiting and in another abdominal pain and vomiting.

With the subsidence of the fever evidences of acute infection in the throat, if they had been previously present, subsided and the enlargement of lymph nodes and spleen gradually receded. The lymph nodes remained palpable, however, for a considerable time and could be felt in several instances from one to six months after recovery.

Recovery was complete and uneventful in all cases.

The unusual feature of these cases and the one which places them in a unique position among the common infections is the degree and type of mononuclear leukocytosis which accompanies the disease. During the first week of the disease and at the time, apparently, of the enlargement of the lymph nodes there occurs an absolute and relative increase in the mononuclear cells of the blood with a slight but distinct decrease in the total number of granular cells. In Cases I and II, which were not seen until convalescence had been established, the total leukocytes were normal in number or even somewhat diminished, but in the other patients they were increased



and the highest counts recorded ranged from 9800 to 26,200. The duration of this high leukocyte count was not great, for it usually lasted but a few days. The course of the mononucleosis is best seen in the accompanying histories (Figs. 1, 2, etc.). They present the variations in the actual numbers of all forms of leukocytes, of the mononuclear cells and of the granular cells. For the purpose of preparing these graphic charts all forms of mononuclear non-granular cells have been estimated in one group and all forms of granular cells in another.

It can readily be seen from these charts that the leukocytosis is dependent entirely upon an actual increase in the non-granular forms of mononuclear cells. This increase was definite by the seventh day of the disease and reached its height usually about the tenth to the fourteenth day of the disease. From this period on there was a decrease in the total leukocyte count with a corresponding reduction in the number of mononuclear cells. Finally the normal relations between the different types of cells were established, but in many instances this required several days or even weeks. With the increase in the mononuclear cells there was an absolute reduction in the number of granular cells, so that instead of the normal number of 4000 to 6000 per cm. there were only 2000 to 4000 cells. With recovery the granular cells increase and finally reach their normal number. These variations in the total number of cells are apparently very characteristic and have occurred in the reported cases as well as in this series.

The histologic appearance of the mononuclear cells of the blood in this disease has been well described and pictured by both Sprunt and Evans and Blaedorn and Houghton. There are three types of mononuclear cells which are found in the blood of all these cases:

1. A small mononuclear leukocyte identical with the small lymphocyte seen in normal blood.
2. Large mononuclear cells identical in appearance with the large mononuclear and transition cells of normal blood.
3. Mononuclear cells of a type not usually encountered in normal blood.

It is the third type of cell that predominates and to which particular interest is attached. In the present cases these cells were somewhat larger in size than the small lymphocytes and contained oval, kidney-shaped, slightly lobulated or Rieder-typed nuclei, staining deeply in Wright's and Hastings's stain. They were usually without definite nucleoli and were often eccentrically placed in the cell. Sometimes the nucleus almost filled the cell but at other times it was surrounded by a fair amount of basophilic protoplasm of ground-glass appearance, which did not contain any definite granules. These cells varied somewhat in size and shape and frequently it was difficult to differentiate them on the one hand from small lymphocytes and on the other from the large mononuclear cells. Occa-

sionally mononuclear cells were observed with eccentrically placed nuclei and deeply staining basophilic protoplasm. Such cells resembled very closely the so-called stimulation form of Türk. In 3 cases in which the oxidase reaction was made the protoplasm of the abnormal cells was found to be free of granules. Though a few of these mononuclear cells presented somewhat the appearance of myeloblasts the absence of the oxidase reaction served to differentiate them from this cell, and it seems highly unlikely that they are derived from the myeloid tissue and much more reasonable to suppose that they arise from true lymphoid tissue. Neither Sprunt and Evans nor Blaedorn and Houghton obtained oxidase reactions in the cells from their cases, and these authors come to the conclusion also that the abnormal mononuclear cell is a derivative of lymphoid tissue.

With convalescence and a decrease in the leukocytes these abnormal cells gradually disappear from the blood.

In no instance was there an anemia associated with the abnormal blood picture.

The clinical course in all the reported cases presents a fairly uniform picture.

The disease has occurred usually in young adults or in adolescents. Curiously enough many of the patients have been medical students or young physicians.

The onset is rather gradual, with malaise, headache and an irregular fever occasionally accompanied by chills. In many instances at the onset there is a pharyngitis, an actual tonsillitis, a tracheitis or a cough. Sometimes the lymphoid tissue of the pharynx becomes much swollen. Very frequently the patients complain of sweating. In a few instances there has been abdominal pain with nausea and vomiting. Rarely the first sign of the disease noticed by the patient has been an enlargement of the cervical lymph nodes. More frequently the cervical lymph nodes became enlarged and tender during the first week of the disease. They may reach 1 or 2 cm. in diameter and are quite firm. In some instances the enlargement is confined to the cervical nodes but frequently the axillary, inguinal, even the epitrochlear and possibly the bronchial, lymph nodes are involved and become swollen, firm and tender. In some cases during the first or second weeks the spleen is enlarged, becomes readily palpable and is tender. By the seventh day the mononucleosis is well marked and from this time until the tenth to the eighteenth day the leukocytes increase in numbers and the mononucleosis advances. The fever, which is often mild and rarely goes above  $102^{\circ}$  or  $103^{\circ}$ , continues irregularly until the tenth to the twentieth day and then gradually subsides. With the fall in temperature the symptoms subside, the lymph nodes recede, the spleen diminishes in size, the leukocytes fall and the mononucleosis gradually disappears (Figs. 4 and 5). Convalescence is rapid and uneventful,

though the lymph nodes may remain palpable for weeks and a slight increase in the mononuclear cells of the blood may persist for some time.

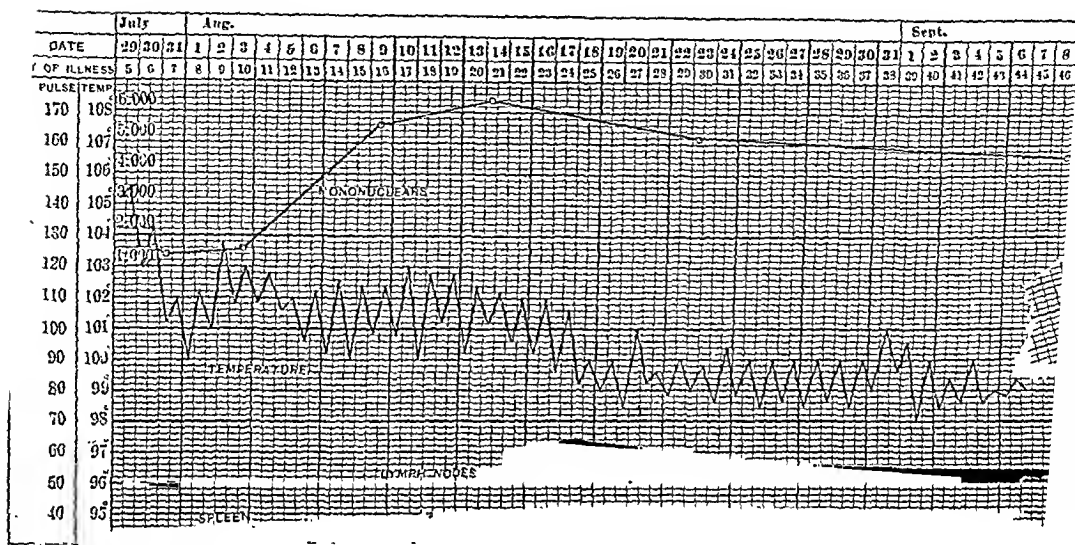


FIG. 4.—Case III. Chart showing temperature curve, changes in absolute numbers of mononuclear cells and variations in size of lymph nodes and spleen during disease.

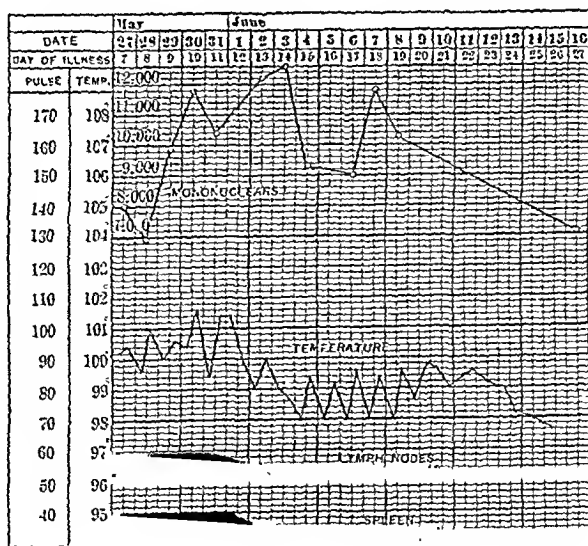


FIG. 5.—Case IX. Chart showing temperature curve, changes in absolute number of mononuclear cells and variations in size of lymph nodes and spleen during disease.

The accompanying charts show graphically the course of the fever and the way in which it precedes for several days the rise in mononuclear cells.

There is almost nothing known about the pathology of the disease. The lymph nodes from 3 of the cases reported by Sprunt and Evans were examined histologically. The sections are reported as being quite similar and as presenting a picture that could not be differentiated, save in the degree of hyperplasia, from lymphatic leukemia. The sections presented no indications of Hodgkin's disease, tuberculosis or lymphosarcoma.

In 2 of the cases reported here lymph nodes were excised and examined histologically. An axillary lymph node removed from P. F. (Case II), on February 16, 1915, presented the following appearance:

"From the left axilla the lymph node has been excised. This on section shows almost complete loss of normal structure. There is marked lymphoid hyperplasia of the germinal centers, the cells of which show karyorrhexic and karyokinetic nuclei. In the lymph spaces between the cords there is active proliferation of the epithelioid cells of the reticulum with the formation occasionally of large uninuclear cells almost of giant size. A few of these large epithelioid cells are also mixed with the cells in the lymph cords. Occasionally an eosinophilic leukocyte is seen. The picture suggests very strongly Hodgkin's disease, though one would scarcely dare to make a definite and positive diagnosis."

A cervical lymph node from Case III presented a picture which simulated in some respects Hodgkin's disease, but was not sufficiently characteristic to allow one to make that diagnosis.

Neither bacteriologic nor serologic examinations has thrown any light on the cause of the disease or served even to indicate whether it is merely an unusual form of reaction to an ordinary pyogenic infection or a disease *sui generis*. In the cases of Sprunt and Evans the stool examinations were negative in all. None showed a positive Wassermann test. In 4 cases blood cultures were made and were negative. Throat cultures were made in 2 cases, one of which showed a nonhemolytic streptococcus. Cultures of the cerebrospinal fluid in 1 case was negative. Animal inoculation of a gland from 1 case failed to disclose a definite etiological agent. Blaedorn and Houghton state that spiral organisms were seen in smears from the throat of three of their four patients.

In the 10 cases presented here blood cultures taken in 7 and in several instances repeated more than once gave no growth of bacteria. The von Pirquet reaction was made in 4 cases and was found negative and the complement-fixation test for tuberculosis was done in one instance with negative result. The Wassermann reaction was negative in the 7 cases which were tested; the Widal reaction was performed in 5 cases and was negative in all. Urine

cultures were made in 2 cases without obtaining a growth of bacteria. Culture from the tonsils and the throat did not yield any constant results. In one instance in which there was tonsillitis *Staphylococcus aureus* was obtained; in another instance *Streptococcus viridans* and *Micrococcus catarrhalis*, in a third instance no bacteria of pathologic significance were obtained, and in a fourth streptococci and staphylococci. Smears from the inflamed tonsils and pharynx of 3 cases showed spirillæ and fusiform bacilli in small numbers.

No evidence of tuberculosis could be discovered in any of the patients. Radiographs of the lungs were made in 6 cases. In one instance (Case II) the bronchial nodes were rather large but not calcified. In one instance the linear markings were thought to be accentuated and in the other 4 cases the lungs were normal. One patient (Case I) several years after his attack developed tuberculous pleurisy, from which he recovered. The other patients have remained well for from one to seven years.

**Discussion.** From the results of this study of these ten patients and the reports in literature one is strongly impressed with the view that these cases represent instances of a definite disease entity. Certainly the clinical picture is sufficiently striking to differentiate these cases from other known forms of acute infections.

The disease has been mistaken for tuberculosis, typhoid fever, Hodgkin's disease and leukemia. In a few instances syphilis was suspected. There is no evidence to show that the condition is related in any way to any of these diseases. The resemblance to leukemia is perhaps most striking, but the early and marked enlargement of the lymph nodes, the absence of anemia and of purpura, and the histological and biological characteristics of the abnormal mononuclear elements of the blood practically exclude the possibility of considering these cases as instances of mild and transient acute leukemia.<sup>1</sup>

There are only a few specific infections such as typhoid, pertussis, malaria, Malta fever and possibly tuberculosis, and intoxications such as those from arsphenamine and tetrachloride poisoning,<sup>17 18</sup> which are known to produce in adults an absolute mononucleosis. Even in these instances the absolute increase in the mononuclear cells is not very great and is frequently insignificant when compared to the considerable mononucleosis encountered in many of the cases recorded here.

It has been suggested that the mononucleosis might be regarded as a peculiar reaction of the individual toward such common types of infection as those caused by streptococci or *Staphylococcus aureus*. Cabot considered that the infection in most of his cases was caused by streptococci. But it has been shown by Sprunt and Evans that an individual who has suffered an attack of "infectious mononucleosis" may subsequently give a perfectly normal polymorphonuclear response to a simple pyogenic infection. There does not seem to be, therefore, any direct evidence to uphold the

assumption that the mononucleosis is an individual characteristic. A much more rational view would seem to be that these cases represent instances of a specific infectious disease presenting very definite characteristics with such an unusual blood picture that this feature serves to differentiate the infection from most other acute infections of known etiology. If the disease is due to a specific agent it seems highly probable, both on account of the frequent and early implication of the upper respiratory tract and the uniform involvement of the cervical lymph nodes, that the virus gains entrance to the body usually through the tonsils or the upper respiratory tract itself, a conclusion that was also reached by Sprunt and Evans and Blaedorn and Houghton.

At the present time the etiologic agent is unknown. Blaedorn and Houghton, who found spiral organisms and fusiform bacilli in smears from the tonsils in three of their four cases, are inclined to regard the disease as a form of Vincent's angina. In none of the cases, however, does the appearance of the inflamed throat or tonsils resemble very closely the conditions seen in Vincent's angina; and though the occasional presence of spiral organisms and fusiform bacilli has been noted, the occurrence of these organisms in small numbers in many forms of throat infection is so common that it would be improper to attach too much importance to such findings. Only three of the patients who had tonsillitis in this series showed spiral organisms and fusiform bacilli in smears. Cultures from the tonsils and the inflamed throats showed such a diverse flora that no one organism seemed to occur with any regularity.

The clinical picture alone suggests very strongly that the "glandular fever" originally described by Pfeiffer is one and the same condition; but until epidemics of infectious mononucleosis are recorded, or until cases of characteristic glandular fever are described in which the blood picture differs essentially from that in "infectious mononucleosis," it will be impossible to settle this question. Pending the settlement of this point, however, the term "infectious mononucleosis" (Sprunt and Evans) is perhaps the best one to employ. It has the virtue of calling particular attention to the blood picture.

**Conclusions.** Ten cases of infectious mononucleosis are described. The relation of this disease to glandular fever is discussed.

The uniform character of this febrile disease and the association of an enlargement of the lymph nodes with a striking increase of mononuclear cells of abnormal type in the blood serve to differentiate the condition from other acute infectious diseases.

If the disease is an entity, as it appears to be, the specific cause is unknown.

It resembles most closely acute leukemia but may be differentiated by many characteristics.

The disease is of short duration and recovery is the rule.

## BIBLIOGRAPHY.

1. Pfeiffer, E.: *Jahrb. f. Kinderh.*, 1889, 24, 257.
2. Korsakoff, K. S.: *Arch. f. Kinderh.*, 1905, 41, 320; 42, 193.
3. Lublinski, W.: *Ztschr. f. klin. Med.*, 1907, 62, 170.
4. Schlissner, F.: *Wien. klin. Wchnschr.*, 1911, 24, 310.
5. Terflinger, F. W.: *Jour. Am. Med. Assn.*, 1908, 50, 765.
6. Jones, G. I.: *AM. JOUR. MED. SCI.*, 1908, 135, 346.
7. West, J. Park: *Arch. Pediat.*, 1896, 13, 889.
8. Tidy, H. L., and Morley, E. B.: *Brit. Med. Jour.*, 1921, 1, 452.
9. Türk, W. M.: *Wien. klin. Wchnschr.*, 1907, 20, 157.
10. Marchand, F.: *Deutsch. Arch. f. klin. Med.*, 1913, 110, 359.
11. Cabot, R. C.: *AM. JOUR. MED. SCI.*, 1913, 145, 335.
12. Hall, A. J.: *Proc. Roy. Soc. Med.*, 1914-1915, 8, 15.
13. Deussing, R.: *Deutsch. med. Wchnschr.*, 1918, 44, 513, 542.
14. Sprunt, T. P., and Evans, F. A.: *Johns Hopkins Hosp. Bull.*, 1920, 31, 410.
15. Blaedorn, W. A., and Houghton, J. E.: *Arch. Int. Med.*, 1921, 27, 315.
16. Morse, P. F.: *Jour. Am. Med. Assn.*, 1921, 77, 1403.
17. Minot, G. R., and Smith, W.: *Arch. Int. Med.*, 1921, 28, 687.
18. Keidel, A., and Moore, J. E.: *Arch. Int. Med.*, 1921, 27, 716.

## THE RELATIONS OF HYPERTENSION TO CARDIORENAL DISEASES.

BY NELLIS B. FOSTER, M.D.,

NEW YORK.

IN the explanation of the vascular disorders associated with nephritis two opposing conceptions have been advocated. These two ideas are that these vascular changes are traceable to some metabolic disorder of which hypertension is a symptom, or second, that there is a primary change in the arterioles which in turn gives rise to hypertension and a consequent train of phenomena. Both ideas were suggested by Bright: "Either that the altered quality of the blood affords irregular and unwonted stimulus to the organ (heart) immediately, or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through distant subdivisions of the vascular system."<sup>1</sup>

Changed in form of expression from time to time, these two conceptions have delimited, nevertheless, the pendulum of opinion even up to the present. Whether in its earliest form as advocated by Traube, or as more precisely stated by Weigert and Cohnheim, the essential idea of peripheral resistance remained the same. From this point of view vascular hypertension and cardiac hypertrophy are compensatory changes in an effort to meet increased peripheral resistance. Those of us to whom this general view made no appeal have from time to time studied the blood by methods either physical or chemical, searching for a clue to "altered quality."

<sup>1</sup> Guy's Hospital Reports, 1836, 1, 338.

Specifically these studies have been directed to the discovery of pressor substances, the action of which upon the arterioles would elevate blood-pressure. As yet no substance peculiar to the blood of hypertension has been demonstrated. These two theories, commonly called the chemical and mechanical theories of hypertension, are in accord in that the cause of the hypertension in both is assigned to a narrowing of the peripheral arterial system. They differ in that one supposes the vessels structurally changed, sclerosed, while the other supposes a vascular spasm. Now an interesting transition has occurred in the relation of those two conceptions under discussion. Whereas formerly a change in the peripheral arteries often observed in nephritis was invoked to explain hypertension, today there are not a few able students who see in hypertension the primary disorder and regard as secondary the changes of a sclerotic character in the vessels. Indeed, some regard chronic nephritis as one of the logical consequences of the sclerosis of the smaller arteries induced by vascular hypertension. It is readily understandable why there should be much confusion in thought among those not actively engaged in investigation of these questions. Especially so, since new theories are apt to be based not so much on particular increases in the evidence but rather they represent a new evaluation of old evidence, a change in point of view.

The present tendency to regard hypertension as the immediate and chief etiologic factor responsible for vascular changes which culminate in nephritis cannot be accepted without considerable reservation. In the first place it is to be recognized that our ideas of the morbid anatomy of vascular and renal disease are based to a very large extent upon the study of tissues from cases past the prime of life. The diseases in question are chronic and slowly progressive and only occasionally do we have opportunity to examine tissues from young individuals. The condition of kidneys or of the blood-vessels in older persons represents a result of many factors, only some of which are known, just as other tissues show changes as age progresses. Various infections—for example, typhoid, scarlet fever, even measles—it is stated produce arterial degenerations which probably leave some scar. This is definite even if the minor intoxications and metabolic disorders incident in most lives are vague and in a sense episodes. Now in the face of known degenerative factors to place the whole blame of vascular disorder upon the strain imposed upon the arteries by hypertension seems to me a position requiring the strongest support in evidence.

Any theory which is proposed to elucidate the confused problem of cardiorenal disease must be inclusive of a varied clinical syndrome and also explain the basic morphological changes in the tissues in accordance with established physiologic laws of the circulation.

It is worth while to examine each hypothesis proposed in the endeavor to find out which clinical facts it explains and also what



facts, if any, it fails to explain. This method is necessary because all of the theories have some evidence in their favor. The inadequacies of a theory are more likely to arise from a disregard of conflicting evidence.

If we assume nephritis to be the primary disorder it is not difficult to explain hypertension and cardiac hypertrophy as sequelæ. All pathologists have agreed that there is in granular kidneys usually a thickening and narrowing of the renal arteries, especially those of finer caliber in glomerular tufts. This condition of affairs in the circulation in the kidneys might produce an increased resistance to blood-flow which would need to be equalized by an increase in the mean arterial pressure if the same rate of blood-flow were to pass through the kidney. In turn the general vascular hypertonus would lead to cardiac hypertrophy. This hypothesis accords with the facts in more than half of the cases of chronic nephritis at autopsy. Furthermore, in not a few cases the most definite and advanced arterial changes are found in the kidney and in some cases only in the kidney. If we could assume that the response of the circulation as a whole to increased peripheral resistance within the kidney would be an increase of mean blood-pressure then this hypothesis seems to be adequate to explain the facts in the majority of cases of chronic nephritis. But when we attempt to generalize and state as a principle that hypertension arises on account of peripheral resistance offered by narrowed vessels in the diseased kidneys then we meet a number of exceptions which are not readily explained. First of all, the degree of vascular hypertension bears no relation to the extent of destruction and pathologic change in the kidney. Loeb<sup>2</sup> endeavored to establish such a relation but Jores<sup>3</sup> quite refuted it. In fact, so far as could be estimated from serial sections of kidneys, cases with the highest blood-pressure may show the least glomerular lesions. Many confirmations of this fact have been offered in the last decade. Nor is there found any closer relation between cardiac hypertrophy and the extent of glomerular lesions. Indeed, there are typical examples of granular atrophy of the kidney in which both the arterial tension and the size of the heart are normal (Jores). These facts have influenced students of this problem to abandon in its original form, at least, the doctrine of structural change in the arteries as a cause of hypertension. Moreover, there are undoubted cases recorded where no lesion of significance could be found in the kidney although there had been persistent hypertension. As a reaction from this theory, students as careful as Krehl have expressed doubt of any direct relation in an anatomical sense between hypertension and nephritis, the hypertension and cardiac hypertrophy being in his mind a result of functional disorders initiated by the nephritis.

<sup>2</sup> *Deutsch. Arch. f. klin. Med.*, 1905, 85, 348.

<sup>3</sup> *Ibid.*, 1908, 94, 1.

Since the doctrine of peripheral resistance due to arteriosclerosis had so many defects in explaining cardiac hypertrophy and hypertension, other interpretations of the facts have been suggested. In 1908, Rose Bradford<sup>4</sup> suggested that a functional high tension in the vessels precedes anatomical change, the increased tension being induced by vasomotor excitation. The vasomotor irritant might possibly be a metabolic product; Bradford suggested urea. A similar conception had been entertained by Senator and others before. And the conception today is familiar, due largely to the support of Allbutt and Houchard.

In its original form this doctrine held that a primary renal disease was accountable for the unknown vasoconstrictor substance which caused hypertension. The cardiac hypertrophy becomes then a consequence of the hypertension, and arteriosclerosis a later result effected by strain. There are many facts which invite a favorable attitude toward these conceptions. One of the most impressive phenomena is the rapidly developing arterial hypertension in acute nephritis. It has been asserted that an increased blood-pressure precedes other signs of acute nephritis. This statement I cannot confirm. The blood-pressures were taken daily on a series of cases of scarlet fever, but with the few cases where a clinical nephritis developed there was not antedating hypertension. A definite hypertension may develop, however, within a week after the onset of the nephritis. In cases of glomerular nephritis in children and young adults it has been noted repeatedly that when recovery takes place the blood-pressure subsides as the other symptoms abate. In these cases, so far as one can judge, there is some intimate relation between the blood-pressure and the fundamental disease. To all appearances, at least, the toxin which causes the nephritis also causes the disorder which induces increased arterial pressure. And in those cases of chronic nephritis developing out of acute nephritis one has very scant evidence to assert that conditions are in any way different. The essential facts clinically are a persistence of the symptoms beyond the usual period; then a gradual change in the type of renal function but with no abatement in the hypertension till death, perhaps two years after the onset of the disease.

There is also experimental evidence favorable to the idea of a relation between elevated blood-pressure and renal function. The reductions of kidney substance performed by Pässler<sup>5</sup> on dogs were followed by an increase in blood-pressure averaging 21 mm. of mercury. It is notable too that these dogs developed a polyuria before hypertension was evident. Janeway<sup>6</sup> was able to confirm Pässler's experiments and accepted his conclusion that the hypertension of nephritis is a consequence of kidney disease.

<sup>4</sup> Allbutt's System, 1908, 5, 580.

<sup>5</sup> Pässler and Heineke: Verhandl. d. deutsch. Path. Gesellsch., 1905, 9, 99.

<sup>6</sup> Proc. Soc. Exper. Biol. and Med., 1909, 6, 109; Harvey Lecture, 1912, p. 214.

As I have mentioned, the original mode of stating this hypothesis of hypertension held the renal disorder responsible for the exciting vasoconstrictor substance, or possibly the metabolic disorder which gave origin to the renal lesions, on one hand, also excited hypertension, as I have stated elsewhere. But for reasons which will be mentioned the hypothesis has gradually undergone alterations. The chief reason for these changes is that long-persistent hypertension is not invariably associated with demonstrable nephritis.<sup>7</sup> As a rule it is, but there are exceptions. Of course it is necessary to bear in mind that every morphological pathologist has to make his own standard for normal for an organ like the kidney, since in adults so few specimens are seen without lesion of some kind. As a result of this necessity it becomes a matter of judgment or individual opinion whether the lesions found in any specimen are more advanced or characteristic of disease than the average for the age of the subject, a very nice question at times. Because of these occasional cases of hypertension without significant renal disease there arose the term *primary* or *essential* hypertension. On what disorder this hypertension depends we confess largely ignorance. There are many opinions but little definite evidence. Nevertheless there is notable a gradual shift to the point of view which sees in the increased blood-pressure a mechanical factor that initiates first arterial or capillary sclerosis and from this vascular disorder nephritis develops as a sequel. Ignoring the omission of an explanation for the most conspicuous symptom, hypertension, this conception is plausible in so far as it accords with an idea that strain on the vessel wall is a causal factor in arteriosclerosis. Does this hypothesis take into account the other accepted causal factors in producing vascular fibrosis and sclerosis, namely, a weakened state of the wall from congenital causes or from infectious disease? The examples of generalized arteriosclerosis with no antecedent hypertension are sufficiently common so that it cannot be held that all cases of sclerosis are due to increased arterial pressure. It is pertinent then to inquire whether there are cases of arteriosclerosis and granular kidney without hypertension.

For reasons already mentioned the lesions found in the kidneys of adults are always open to several interpretations. On this account the occasional juvenile case is of the greatest interest. In 2 cases which have come under my notice, nephritis developed in early life and death occurred before the twentieth year. These cases were peculiar in the absence of any known infection as a cause for the nephritis and a normal blood-pressure throughout the disease. At autopsy the kidneys were smaller than normal, and granular. Sections showed the ordinary picture of chronic

<sup>7</sup> Ophüls: Arch. Int. Med., 1912, 9, 156. Lohlein: Ergeb. inner. Med. u. Kindh., 1910, 5, 411.

nephritis with fibrosis of some glomerula, thickening of the vessels of the glomerular tuft and considerable overgrowth of fibrous tissue throughout. An interesting fact in these cases was the very suggestive history of vascular disease in the families. In one the father and grandfather had died of "nephritis"; in the other the father had died of apoplexy early in life.

The only deduction drawn from these cases is that arterial and renal degeneration may develop without antedating hypertension. The type of renal lesion in these cases was not, in my opinion, essentially different from that often seen with hypertension. Further, these cases illustrate, possibly, one mode of development of arteriosclerosis, that dependent upon an inherent predisposition. In what precisely that inherent taint consists we do not know, but there seems little doubt of its occurrence, the "bad rubber of the arteries" referred to by Osler.

But these cases of juvenile vascular disease and nephritis do not controvert the factor of strain as a causal agent in arteriosclerosis, because on the inherently weak bloodvessel the normal blood-pressure may impose quite as much strain as an increased pressure does on a sound vessel. This fact is sometimes overlooked in our evaluation of stress in etiology.

Of course, it is a notorious fact in every pathological laboratory that we see from time to time cases where there had been no suspicion of clinical nephritis during life, and yet the kidneys at autopsy are found to be sclerotic and atrophic to a high degree and the renal vessels definitely diseased. But in these cases, even when they have been under observation without at any time detectable hypertension, there still remains the suspicion that at some time in the past, perhaps, there had been a period of elevated blood-pressure, enough elevated and for a period long enough to initiate a process of vascular sclerosis. On that account the juvenile cases are more impressive because comparatively free of suspicion of this sort. Nor are these cases excessively rare. Primary vascular disorder is not apt to come to mind as an explanation for impaired health in younger subjects and searching examination is not instituted for its detection.

The first point, then, to which my evidence brings support is that vascular sclerosis and nephritis of the vascular type can arise without antecedent hypertension.

Now and then a case comes under observation with the history that at some time in the past there had been a period of high blood-pressure. Occasionally the physician is known and confidence can be given to the history. Either because of an altered mode of life or due to some natural readjustment, the hypertension of past years has disappeared, not on account of failing heart, but, on the contrary, synechronous with improvement in general health. Two cases of this sort have come to my attention where I have no right

to doubt the correctness of the history. While neither of these cases presents any sign or symptom today of vascular disease or nephritis, one is forced to confess that a considerable degree of both may escape detection. A third case of hypertension, of at least four years' duration, was seen several times during the later period of life. He died of pneumonia at the age of twenty-four, and opportunity for postmortem study was given. In this case there were a few small atheromatous areas in the aorta, but the smaller arteries and the arterioles of the kidney, pancreas and spleen were quite normal. There was no nephritis. I mention the spleen and pancreas because sclerosis of the arteries is apt to show earliest in these organs. Now one may quite naturally object that the absence of sclerosis was due to resistant arteries of a young subject. But if this be true, and it possibly is, then we introduce another factor besides the strain of hypertension in the production of arteriosclerosis—namely, the age of the patient, and age implies degenerations and changes in metabolism.

The evidence presented in these few cases appears to me to indicate that vascular disorder and nephritis may occur without antecedent hypertension; next, that hypertension can persist for a considerable period of time, at least, and yet leave no significant, detectable change in the structure of either the arterioles or the kidney. Yet there is no doubt that hypertension, nephritis and vascular disease are commonly associated, and the sole question is whether this association is one of direct and necessary cause and effect. The exceptional case, where either hypertension occurs alone without sclerosis, or sclerosis alone without hypertension, casts serious doubt upon any necessary or causal relationship between these phenomena.

It has been assumed for the sake of clarity in this discussion that arteriosclerosis in its broadest sense can be induced by arterial hypertension operating over a period of time. No such assumption is justifiable, however. While there is a general consensus of opinion concerning the lesions in arteriosclerosis there is no unanimity as to etiologic factors, nor even as to the order in which lesions arise in the vessel coats. Some regard the lesions in the media as primary; others, those in intima. Hence, we cannot expect accord respecting the factors which induce these lesions. The thickening of the vessel wall in arteriosclerosis is a result produced by degenerative changes, usually of a fatty type, sclerosis, calcification and inflammatory processes. (Marchand<sup>8</sup>). Various pathologists have been impressed by some one of these processes, often to the exclusion of the others. So Jores seems most interested in connective-tissue growth of the intima. He regards the process as physiologic up to a certain point, beyond which it is designated

as a departure from normal rather than pathologic. The effect of arterial tension in stimulating this process is pure speculation supported by no definite evidence. And Jores admits in discussing localized arteriosclerosis of the branches of the renal artery that the sclerotic changes with hyperplasia of the internal elastica are absent in some cases of chronic nephritis with granular kidney. Nor are these changes present in acute forms of nephritis in which there is an elevated blood-pressure. From purely morphological study of arteriosclerosis it is difficult to understand how lesions so various can be nicely traced to their immediate inciting agent. In a careful review Ophüls<sup>9</sup> points out the relation between arteriosclerosis in general and various infections and intoxications, and states his opinion that the renal lesions so often associated with arteriosclerosis are not interdependent with it but rather produced by the same causative agent. Nor is there a direct causal relation between hypertension and arteriosclerosis. From the experimental side the best-known work bearing on the relation of hypertension to arteriosclerosis is that of Klotz,<sup>10</sup> who used adrenalin. That adrenalin produces lesions comparable to some types of human arteriosclerosis seems to be accepted. But whether this result is due to the blood-pressure-raising effect or not is in doubt. When the hypertensive effect of adrenalin is prevented by the administration of vasodilators along with adrenalin the same arterial lesions are produced. So it appears that it is some toxic effect of adrenalin rather than the mechanical effect of hypertension which causes the arterial lesions.

In a review of the subject of arteriosclerosis, MacCallum<sup>11</sup> concludes that elevated blood-pressure acting alone produces little or no change. At most it seems to predispose to imbibition of excessive lipoids in the intimal layer.

Interesting especially in this relation is the experimental production of arteriosclerosis by means of changes in the diet. These changes have been in the directions of excesses in protein<sup>12</sup> and excesses in lipoids, chiefly cholesterol. Anitschkow,<sup>13</sup> whose studies have been most searching, found that heightened blood-pressure alone failed to induce arterial changes in experimental animals, but that characteristic lesions appear in the vessel wall following cholesterol feeding. When cholesterol feeding is combined with measures which elevate blood-pressure, smaller amounts of cholesterol induce lesions than when the blood-pressure is normal.

Time is not available to discuss in detail the considerable mass of evidence relating to dietetic experiments. The sum total of

<sup>9</sup> Stanford Univ. Publ., 1921.

<sup>10</sup> Jour. Med. Research, 1915, 31, 409; 32, 27; 1916, 34, 41.

<sup>11</sup> Physiol. Rev., 1922, 2, 70.

<sup>12</sup> (Newburgh.) Arch. Int. Med. 1919, 24, 1921, 28, 1.

<sup>13</sup> Ziegler's Beiträge, 1913, 56, 379; 1914, 59, 306; also Knack, Virchow's Arch., 1915, 220, 36.

this evidence appears to be that certain foods, either directly or indirectly, act as toxins, and in that respect are analogous to adrenalin and to toxins of bacterial and metabolic origin. Hypertension as a purely mechanical factor is not adequate to produce arteriosclerosis. It is only operative when accompanied by a nutritional disorder.

Now the peculiarities of hypertension as a symptom in the several disorders which I have mentioned make it very unlikely, at least, that any structural disorder so definite and permanent as a fibrous change can be held accountable for it. The evidence already presented would indicate that hypertension can persist for considerable periods, years in young individuals, without causing detectable changes in the smaller vessels. A third possibility exists, namely, that hypertension and vascular disease, though not interdependent, may both alike be induced by a single remote cause. Were this ultimate cause a toxin its effects would vary in different individuals, depending upon individual peculiarities and predispositions. In some sclerosis might result early, in others hypertension only, in many both synchronously. Implicit in this hypothesis is not only a spasm of the bloodvessels but an injury to them as well.

This frankly speculative idea was suggested by the effects on tissues of a toxic base isolated several years ago from uremic blood. The most conspicuous of these effects was noted in the bloodvessels of the brain and kidney. A natural inquiry here, then, would be, have we in the realm of human pathology any analogous disease where an increase of blood-pressure is a conspicuous symptom of an intoxication? Since the nature of eclampsia is unknown the analogy may be only apparent, but two conspicuous and constant signs in eclampsia are hypertension and albuminuria. Conceivably an intoxication of less severity acting over a long period might induce either nephritis or an injury to the bloodvessels or both.

Using the term arteriosclerosis in the broadest sense the chief factors which are supposed to be operative in its production are degeneration of the vessel wall and stress. This weakness of the wall may be from inherited defect or it may be the result of injury from disease, infections and metabolic intoxications. In any case the reaction in the vessel is primarily one of repair—a thickening of the vessel wall. These factors do not exclude sclerosis with normal blood-pressure and they indicate conditions under which an elevated blood-pressure would be most favorable to the production of sclerosis.

When we study hypertension physiologically it seems doubtful if its mode of production is invariably the same. Accordingly it is doubtful whether the remote causal factors are always the same. Conceivably an increase of the mean blood-pressure may

result either from an increased output of the heart or an increase in the peripheral resistance to the flow of blood. Increased peripheral resistance would elevate primarily the diastolic pressure; increased ventricular output, without change in the peripheral arteries, would affect mainly the systolic pressure. Now clinically we note as a rule that when the systolic blood-pressure is elevated the diastolic is also above normal. But this is not invariably the case.

In acute glomerulonephritis I have observed that the first abnormal elevation of the systolic blood-pressure is associated with a proportionate rise of the diastolic also. The only interpretation possible is that there is an increased peripheral resistance. Where this resistance is one cannot say, of course; but that it develops so early in the disease may be of such marked degree and subsides along with other symptoms points to a functional causation related to the primary disorder. When acute-glomerulonephritis becomes chronic there is a continuation of the relation between systolic and diastolic pressures. Since ordinarily chronic nephritis develops insidiously opportunity seldom arises to observe a case in its early stages, or perhaps, more correctly, we lack the ability of detecting the disease. Occasionally one has opportunity to observe the transition of parenchymatous nephritis into the chronic interstitial type of nephritis. In one of these cases which was under observation in hospital for months the first indication that suggested what was taking place was a gradual fall in the specific gravity of the urine. Two months later the systolic blood-pressure began to range over 140 mm. of mercury and the diastolic over 90. Here again systolic and diastolic pressures rose apparently together. In six months there was definite hypertension. A possible explanation in these cases is that the initial rise is diastolic and that the systolic rise is an adjustment to compensate; hence the cardiac hypertrophy. This course of events does not support the idea that the renal lesions are secondary to the hypertension in any sense.

Now there is another clinical manifestation of hypertension of quite a different variety. That is an abnormal systolic pressure with the diastolic within normal range. One sees this seldom; possibly it is an early stage of a disorder, and obviously if the systolic becomes considerably raised the diastolic must rise also if circulation maintain its integrity. In the few cases where I could control my observations the systolic tension was constantly between 140 and 150 mm. of mercury, the diastolic never over 80. One wonders what would be the effect on blood-pressure of the idiopathic cardiac hypertrophies occasionally observed at autopsy.

A third clinical type is characterized by a disproportionate elevation of the systolic and diastolic pressures. The systolic may fluctuate between 160 to 180 mm. of mercury while the



diastolic is more even, around 90 to 100. Another characteristic is the remarkable variation of the systolic pressure even when the patient remains at rest in bed. Now the fact that this type of curve is apt to be found in certain types of individuals or at certain periods of life, and may be transitory in some cases and in others cured, strongly speaks for purely vasomotor origin, the vasomotor instability resulting from metabolic disorders or congenital defects. A functional origin for this type of hypertension does not exclude at all the possibility that its persistence might lead to organic lesions; especially might this be the case if the exciting cause were a metabolic disorder.

Mention has been made several times of the possibility of inherent peculiarities in an individual which either develop into or predispose him to vascular disease. This is an idea supported only by the most general sort of evidence, and yet there are facts sufficiently striking to excite interest to further study. We are no longer accustomed to speak of an apoplectic habitus; but it is a habitus not attainable to all by mere overindulgence in food. Now the chief causes of death in overweight persons, according to the American Actuarial Association, are, in order, apoplexy, heart disease, nephritis. Over one-half of the cases of hypertension are definitely overweight. Excessive weight is not simply a matter of food. It is becoming increasingly evident, as Gräfe<sup>14</sup> indicates, that obesity is a disorder of metabolism. The tendency seems often hereditary. Vasomotor instability and circulatory disorders related thereto have gained renewed attention since the war. Cardiac hypertrophy without assignable cause in young men has been one of the riddles. Alvarez<sup>15</sup> found hypertension not a rare sign in a rather definite type of individual associated with cardiac enlargement and irritability. The same type apparently is detected by Cobb<sup>16</sup> in the examination of individuals from a neuropsychiatric point of view. Here nervous instability, tachycardia, blood-pressure variations and albuminuria were the striking signs.

**Summary.** One can find no adequate evidence for belief that hypertension is a predominant factor in the causation of arteriosclerosis. Even though some types of nephritis may possibly be of vascular origin their genesis cannot be traced through arteriosclerosis to hypertension. But while there is no direct interdependence of these organic changes, there are many facts suggestive of the same causative agent producing both organic changes.

Our present knowledge seems to indicate in a most general way that organic change in the kidneys and vessels may arise in diverse manners, the least indefinite of these being through intoxications of infectious origin. There are suggestions that intoxications

<sup>14</sup> Deutsch. Arch. f. klin. Med., 1920, p. 123.

<sup>15</sup> Reports of Hooper Foundation for Medical Research, 1918-1919, 4.

<sup>16</sup> Jour. Indust. Hyg., 1922, 3, 309.

resulting from abnormal metabolism may have a similar effect. These intoxications produce early only functional disorders chiefly referable to the nervous system. When persistent they induce organic changes affecting the bloodvessels and kidneys.

In a subject so confused as that of hypertension in its relation to arteriosclerosis and nephritis it is best that our ideas remain fluid rather than crystallized into conceptions based as they must be at present on assumptions and speculations. We need first of all a larger range of clinical facts.

## LONG-CONTINUED OBSERVATIONS ON THE VITAL CAPACITY IN HEALTH AND HEART DISEASE.\*

BY JOSEPH H. PRATT, M. D.,

BOSTON.

MR. JOHN HUTCHINSON, surgeon, the inventor of the spirometer, applied the term "vital capacity" of the lungs to the "greatest voluntary expiration following the deepest inspiration." He showed definitely that the vital capacity varied with height, weight, age and disease. As his statistics have not been republished by any recent writer and as his series of observations is much the largest recorded I have prepared two tables from figures given in his original communication.<sup>1</sup>

TABLE I.—INFLUENCE OF HEIGHT ON VITAL CAPACITY  
HUTCHINSON'S OBSERVATIONS ON 1923 MALES.

Feet and inches.		Centimeters		Vital capacity in centimeters.
5 feet to 5 feet 2 inches		150	to 155 cm.	2900
5 " 2 inches to 5 feet 4 inches		155	to 160	3150
5 " 4 " 5 " 6 "		160	to 165	3400
5 " 6 " 5 " 8 "		165	to 170	3725
5 " 8 " 5 " 10 "		170	to 175	3950
5 " 10 " 6 "		175	to 180	4300

In Table I the effect of increased height in increasing the vital capacity is clearly shown. Hutchinson tested 2130 individuals, of which all but 26 were males. There were 60 cases of disease, chiefly phthisis pulmonum. The persons examined were all sorts and conditions of men including gentlemen, paupers, artisans, sailors, soldiers, policemen, printers and pugilists.

\* Read at the Meeting of the Association of American Physicians, Washington, D. C., May, 1922.

<sup>1</sup> Hutchinson, J.: On the capacity of the lungs and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer, *Medico-Chirurgical Transactions*, London, 1846, 29, 137-252.

In a series of 1775 cases he studied the effect of age on vital capacity. He found the maximum vital capacity between the ages of twenty-five and thirty-five.

TABLE II.—INFLUENCE OF AGE ON VITAL CAPACITY (HUTCHINSON).

Age.	Cases.	Vital capacity in centimeters.
15 to 25	774	3425
25 to 35	589	3500
35 to 45	264	3225
45 to 55	92	3050
55 to 65	56	2850

Between the age of fifteen and twenty-five it was almost as great. If 3500 the average vital capacity between twenty-five and thirty-five be taken as 100 per cent, the average in the preceding period of ten years will be 98 per cent. A marked fall occurred after forty-five years of age according to his observations, and between fifty-five and sixty-five it dropped to 71 per cent. It should be noted that over three-quarters of his cases were under the age of thirty-five. It is important in considering the relation of height to vital capacity to know that most of his determinations were made on young men.

Peabody and Wentworth<sup>2</sup> reported in 1917 the vital capacity in a series of 96 normal men, and 44 normal women. They were chiefly medical students and nurses. The average age was probably between twenty and twenty-five years. Their figures for males were considerably higher than those obtained by Hutchinson (see Table I). The average vital capacity for men 6 feet tall or over was 5100. For men 5 feet 8½ inches to 6 feet in height it was 4800, while men less than 5 feet 8½ inches tall and over 5 feet 3 inches had an average vital capacity of 4000.

Peabody and Wentworth showed the influence of sex on vital capacity, confirming observations of Arnold, made many years before. It is lower in women than in men of the same height. The average vital capacity in women over 5 feet 6 inches tall was 3275; in women varying in height from 5 feet 4 inches up to and including 5 feet 6 inches it was 3050; in still shorter women, 5 feet 1 inch to 5 feet 4 inches the average was 2825 cc.

West's studies show strikingly the lower vital capacity in women. In 75 out of 85 normal men he examined the vital capacity was 4000 or more; while 42 in a series of 44 women had a vital capacity below 4000 cc.

Hewlett and Jackson,<sup>4</sup> in their examination of 400 healthy male students of Leland Stanford, Jr., University found the average vital capacity to be the same as that obtained by West in his study

<sup>2</sup> Arch. Int. Med., 1917, 20, 443.

<sup>3</sup> Ueber die Athmungsgrösse des Menschen, Heidelberg, 1855.

<sup>4</sup> Arch. Int. Med., 1922, 29, 515.

of Harvard Medical students. Oxford students, as Schuster<sup>5</sup> showed had an average vital capacity about 7 per cent lower and Hutchinson's subjects more than 20 per cent lower.

METHODS EMPLOYED IN THE PRESENT STUDY. I have used the wet spirometer made by the Narragansett Machine Company of Providence, R. I. This has been tested and found to give trustworthy readings.

The observations recorded have been made by me personally. I have taken pains to instruct each person examined in the use of the instrument. Three or more trials were made. Each one was encouraged to inhale and exhale the maximum amount of air. The highest reading was taken as the vital capacity. Each subject was watched carefully during the test and any error noted was corrected. Toward the end of expiration some persons draw in a little air, and blow the spirometer to a higher level than is possible for them with a single inspiration. This error can be eliminated by rejecting all readings in which the upward movement of the spirometer is not continuous.

Most of the heights recorded in this paper were taken without removing the shoes. This increases the height of men usually from  $\frac{3}{4}$  of an inch to a full inch, but with women the shoes may increase the height from 1 inch to  $2\frac{1}{2}$  inches. As the heels vary so much in height I now take this measurement in stocking feet. The heights given by Hutchinson include the shoes, while Peabody and Wentworth's are for bare feet. The weight of my subjects include the clothes. I allow for this one-eighteenth of the weight for males and one-twentieth for females.

As a standard I have taken the one recommended by West<sup>6</sup> as he found a more constant relationship existed between the vital capacity and the body surface area than between the vital capacity and the height, weight or chest volume. It is determined by dividing the vital capacity by the surface area of the body. The latter is calculated by Du Bois' formula. By means of the graphic chart published by Du Bois and Du Bois<sup>7</sup> the surface area is easily determined when the height and weight are known.

According to West the normal vital capacity for men is 2.5 liters per square meter of body surface, for women 2 liters. Such a standard, as Hewlett and Jackson point out, is based on the assumption that there is a simple relation between the vital capacity and some body measurement. Hewlett and Jackson have obtained a formula for calculating the vital capacity from the height and surface area of the body. It introduces an additional constant as is usual in statistical formulas but is applicable only to college students. I have studied the effect of age on vital capacity in a

<sup>5</sup> *Biometrika*, 1911, 8, 40.

<sup>6</sup> *Arch. Int. Med.*, 1920, 25, 306.

<sup>7</sup> *Ibid.*, 1916, 17, 863.

series of 100 men who showed no evidence of disease of the heart or other organs at the time of their examination. The results are presented in Table III.

TABLE III.—PERSONAL OBSERVATIONS ON THE INFLUENCE OF AGE ON VITAL CAPACITY IN 100 NORMAL MEN.

Age.	No. of persons.	Average height in cm.	Weight in kgm.	Body surface area in square meters.	Average vital capacity in cc.	Average per cent of West's standard.
10 to 20	9	157	47.0	1.47	3125	82
20 to 30	14	173	58.6	1.72	4500	105
30 to 40	23	166	67.1	1.75	3950	90
40 to 50	20	171	69.0	1.81	3775	83
50 to 60	20	170	73.9	1.85	3825	83
60 to 70	11	169	69.8	1.80	3300	73
70 to 80	3	172	69.9	1.82	2525	56

The vital capacity is definitely influenced by the age of the subject. It reaches its maximum in the third decade. The table shows clearly that in the fourth decade the average vital capacity falls slightly. Hutchinson found that the decline began between the age of thirty-five and forty-five years. My averages at all ages are higher than those obtained by Hutchinson. For this I have no explanation to offer. A marked lowering in the vital capacity was not noted in my series until after the age of sixty. The 11 men who were between the age of sixty and seventy when tested showed an average vital capacity of only 73 per cent of West's standard. Above the age of seventy I have examined only 3 men with apparently normal hearts. They had no shortness of breath on exertion, but their vital capacity was much reduced, being only 56 per cent of the normal. The number of cases in this decade is too small to permit of drawing any conclusions from the figures given. When more persons above seventy are examined the average percentage may be lower or higher. I think it will probably be higher, in light of the following observations. One of the men included in the seventh decade in this table has now reached the age of seventy and his percentage of the normal is 65. I have seen a patient of seventy-two with definite cardiosclerosis whose vital capacity was 3050 cc which was 56 per cent of the standard. I know of a vigorous man of eighty whose vital capacity was 3200, which was 70 per cent of his normal.

Individuals may vary considerably from the average vital capacity for their age, height and weight, and yet no disease be present. Hutchinson thought from his study that a reduction from the normal was a valuable sign in the diagnosis of early phthisis. Subsequent investigators found that the individual variations were too great to make the vital capacity determination of value in the recognition of the early stage of this disease. Furthermore the

vital capacity test of the same person may vary from time to time. I have recorded the amount of variation of the vital capacity in 9 persons with apparently healthy hearts and lungs over periods ranging from fourteen months to three years and four months (Table IV). Although the 7 men in this group were urged to make a maximum exertion at each test, and they apparently did so, the variation was considerable, ranging from 100 to 550 cc.

TABLE IV.—VARIATION OF THE VITAL CAPACITY DETERMINATIONS OVER PERIODS RANGING FROM ONE TO THREE YEARS.

Name.	Duration of observation.	No. of tests.	Vital capacity.		Variation. cc.
			Maximum cc.	Minimum cc.	
Mr. H.	3 years 5 months (Nov. 17, 1918 Apr. 5, 1922)	8	2825	2500	325
Mr. L. D.	3 years 4 months (Dec. 3, 1918 Apr. 10, 1922)	3	3650	3100	550
Mr. A. K.	2 years 8 months (Sept. 5, 1918 May 20, 1921)	3	4500	4300	200
Mr. F. D.	2 years 4 months (Dec. 30, 1919 May 8, 1922)	8	3300	3000	300
Dr. R.	2 years 3 months (Dec. 13, 1919 Apr. 6, 1922)	9	3700	3300	400
Miss E. L.	2 years 2 months (July 1, 1919 Aug. 30, 1921)	3	1800	1775	25
Mrs. T.	2 years 2 months (Apr. 15, 1920 June 7, 1922)	8	1450	1400	50
Mr. F. F.	1 year 7 months (Nov. 11, 1920 June 2, 1922)	3	3350	2900	450
Mr. R. A.	1 year 2 months (Jan. 20, 1919 Mar. 25, 1920)	2	2650	4500	150

In the period covered by these tests there was no decrease that could be attributed to increasing age. The age of 1 of the men was sixty-six when his vital capacity was first determined. It was then 2800 cc, at sixty-eight it was 2550, at sixty-nine it had risen to 2700. A year later when just seventy years of age for the first time in the series of eight tests he was able to expel 2825 cc of air into the spirometer. In none of these people was there either a steady fall or rise in the vital capacity. The change as shown by plotting the curve was an irregular fluctuation. The vital capacity in the different tests made on the 2 women showed very little variation. In 1 of these the range was 50 cc and in the other only 25 cc.

On 1 person my observations of the vital capacity span a period of sixteen years. The tests were all made on the same spirometer. The patient, S. R., had early active pulmonary tuberculosis in 1905. At the time the first determination of the vital capacity was made there was dulness to the second rib of the right lung

anteriorly and rales were present over this area. His vital capacity was then 74 per cent of the normal. He was thirty-four years of age. The average vital capacity in the fourth decade in my series of 23 was 90 per cent. The lowest percentage recorded by West among his 85 normal men was 82 per cent, but West's man with this low percentage was only twenty-three years of age. It is impossible to decide whether the vital capacity was normal for my patient or reduced by tuberculous infiltration of the lungs. In April, 1906,

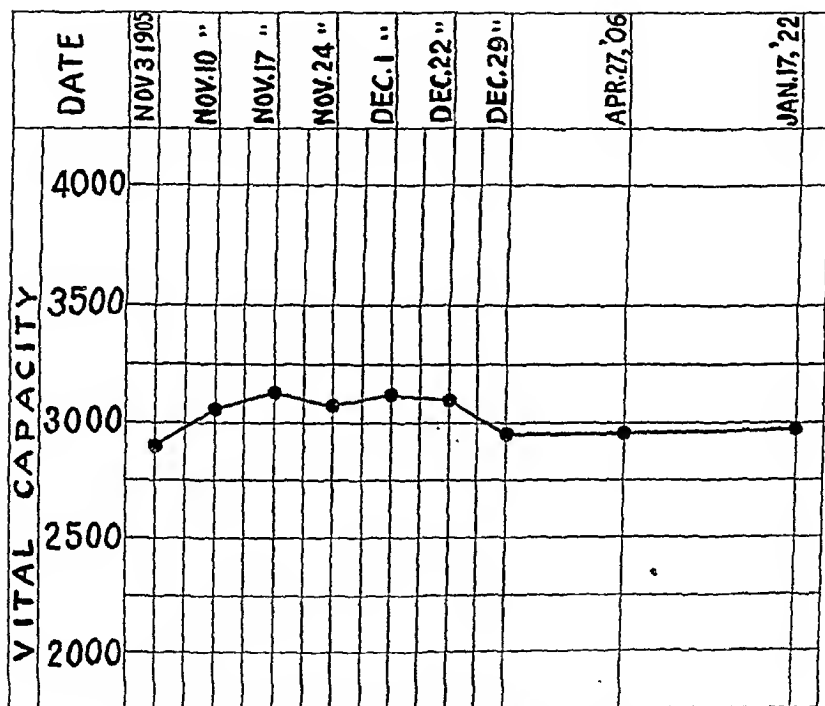


CHART I.—Vital capacity record covering a span of sixteen years.

the symptoms and signs of active pulmonary tuberculosis had disappeared, but his vital capacity was practically the same, 75 per cent. Sixteen years later it was 72 per cent of the normal. At his present age of fifty it is still low for his years. He has been well and working since his recovery in the spring of 1906 to the time the last test was made, January, 1922. The nine observations made on this man showed a variation in the vital capacity of only 125 cc (Chart I).

Peabody<sup>s</sup> showed that the vital capacity was low in cardiac insufficiency because of the inability to increase the depth of breath-

ing in the normal manner. He and his associates<sup>29</sup> found that when the patients improved under treatment there was a rapid and marked increase in the vital capacity, and also that an increase of the cardiac weakness was accompanied by a further fall in the vital capacity.

I have compared the vital capacity in 100 persons, both men and women who had organic heart disease with 100 other persons who had normal hearts. The results of this analysis are presented graphically in Chart II.

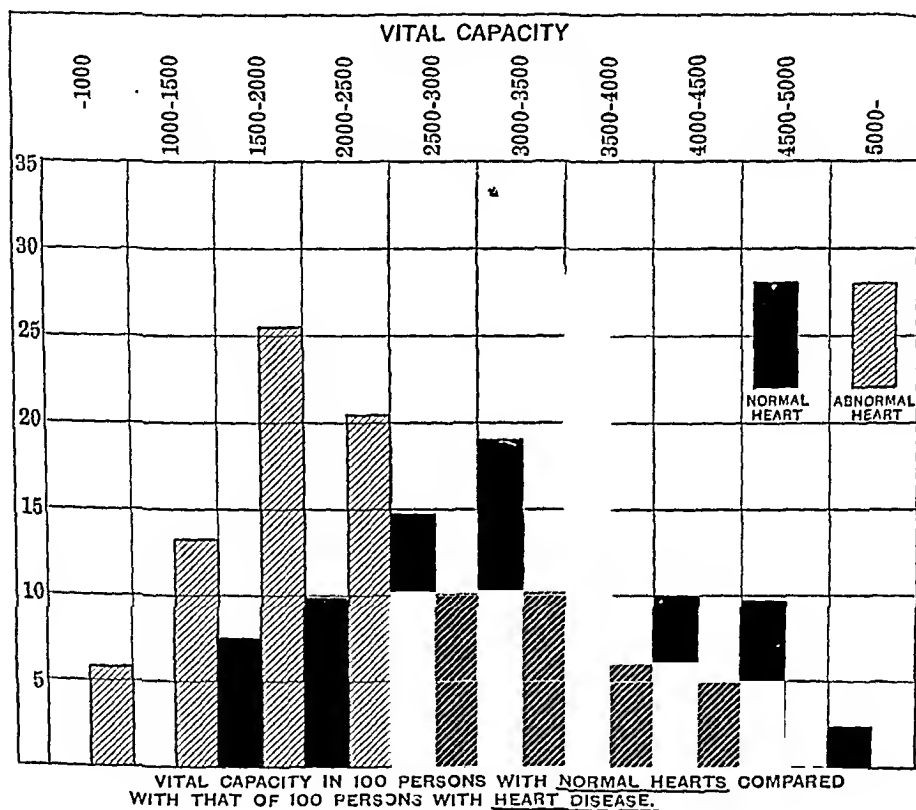


CHART II

The mean vital capacity of the 100 persons with normal hearts was between 3500 cc and 4000 cc, while the mean for these with abnormal hearts was between 1500 cc and 2000 cc. No one with a healthy heart had a vital capacity below 1500 while 18 per cent of those with heart disease had a vital capacity below this level. No one with a diseased heart had a vital capacity above 4500 cc and only 5 of the 100 above 4000 cc; 11 per cent of those with healthy hearts had a vital capacity above 4500.

Seventy-seven of the 100 persons with abnormal hearts had cardiac insufficiency of the congestive type. Dyspnea on exertion or edema

<sup>29</sup> McClure, C. W. and Peabody, F. W.: Jour. Am. Med. Assn., 1917, 69, 1954.



was present. Sixteen presented no evidence of cardiac weakness. The average vital capacity of the males in the first group was between 2500 and 3000, of the women in this group between 1500 and 2000 cc. In the second group, without evidence of cardiac weakness, the average vital capacity among males was 1000 cc more than in the first group, but among the females the average was just as low, 1500 cc to 2000 cc, as in group one. Seven patients, all males, had angina without breathlessness. Their average vital capacity was between 3500 cc and 4000 cc.

Since the spring of 1917 I have followed the variation in the vital capacity of all cases of heart disease that have been under my care. When cardiac insufficiency of the congestive type has existed the vital capacity has followed closely the change in the clinical condition. It has proved to be a good index of the amount of reserve power possessed by the heart.

In 4 cases the vital capacity has been determined over periods ranging from nineteen months to nearly five years. The clinical condition in cardiac insufficiency is more clearly shown by charts of the vital capacity readings than by the graphic representation of any other measurement, or any other record such as a statement of the amount of effort that can be made without dyspnea.

CASE I.—James M., aged forty-four years in 1917. Seen in the Cardiac Clinic of the Massachusetts General Hospital. He had mitral stenosis of rheumatic origin with auricular fibrillation. When the vital capacity was first determined in 1917 he could not walk 100 yards without stopping for breath. Apex rate 125, radial rate 105. His vital capacity was 1300 cc. which was 32 per cent of the normal (West's standard). The next week he returned to the out-patient department. He had taken 2.1 grams of active digitalis leaf. He felt better. Two days after beginning to take the digitalis (0.1 gram, 3 daily) he had a free diuresis. After this occurred he had less dyspnea. His vital capacity had increased to 41 per cent.

March 1, 1917. Patient has felt quite well the past few days. Heart rate 80, deficit 10. Vital capacity 48 per cent. Resumed work today as assistant agent at railroad station, March 17. Has worked steadily for two weeks. Can now walk a quarter of a mile without stopping. Heart rate: Apex 52, radial 52.

Vital capacity continued to rise under digitalis treatment as shown by the chart until on April 7, 1917, it was 54 per cent. On May 19, 1917, the vital capacity was 52 per cent. He stated at this time that he could walk a mile without shortness of breath. Pulse 66. No deficit.

When next seen over two years later on November 31, 1919, he presented evidence of severe cardiac weakness. He said he was unable to walk 200 yards without stopping. For two months his

exercise had been restricted by breathlessness. He coughed a good deal and he said that he slept poorly and complained of pain in the region of the liver. Slight swelling of the ankles had been noticed several days previously. The liver was swollen and tender and there was fluid in the chest (hydrothorax). The vital capacity had fallen to 1000 cc or 24 per cent. The pulse was 72, no deficit. During the following week he took 3.3 grams of digitalis leaf. His vital capacity rose to 37 per cent. Pulse 56, no deficit. December 29, 1919. Marked dyspnea even at rest. Has taken no digitalis for four weeks as his local doctor said he would be better off without it. Apex rate 108, radial 76.

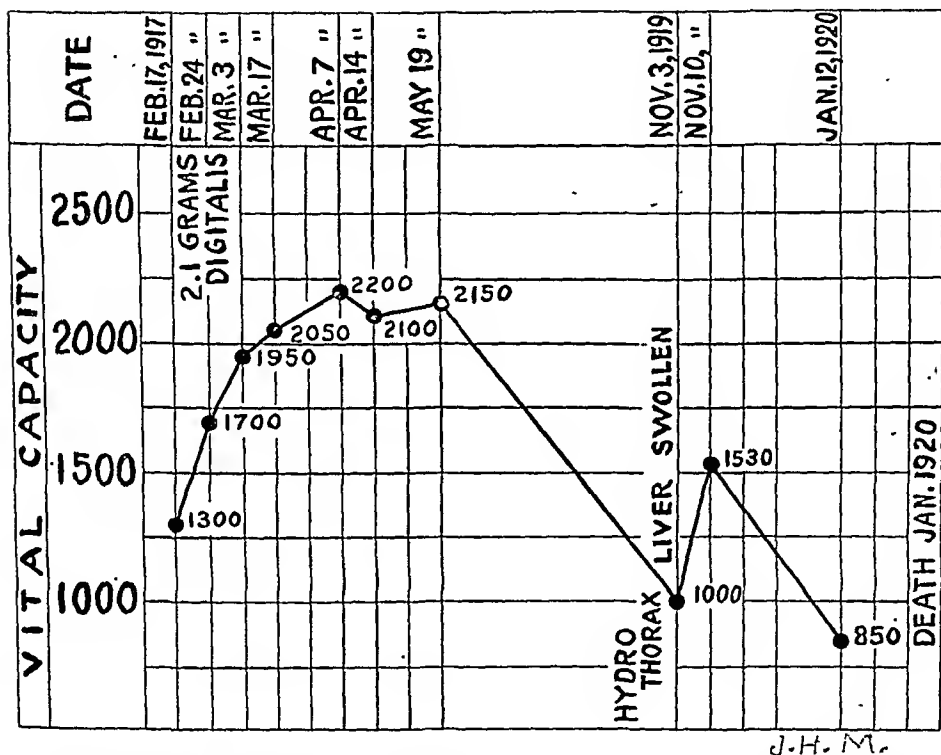


CHART III. Case I.—Mitral stenosis with auricular fibrillation. Improvement from digitalis without bed rest. Record of vital capacity for period of nearly three years.

On January 12, 1920, he returned to the clinic in very bad condition. In spite of having taken 4 grams of digitalis leaf during the previous fortnight the vital capacity had fallen to 850 cc which was 21 per cent. The apex rate was 120, the radial 90. Death occurred a few days later.

The chart shows an increase of 750 cc in the vital capacity which must be attributed to digitalis as he was given no other treatment. He took no regular rest and resumed work before the pulse deficit had disappeared. His vital capacity rose in three months to 54 per cent of the normal. Among 19 ambulatory cases of heart disease

in which I followed the change in vital capacity resulting from treatment only 1 other case showed as marked a rise. The effect of bed rest, measured by the increase in vital capacity has been much greater.

When the patient returned over two years later with his heart greatly weakened it will be noted that although he stated that he could walk further than in February, 1917, before he had to stop, the vital capacity was lower. Rapid improvement with a rise of 530 cc in the vital capacity in one week followed the employment of digitalis and rest. Omission of digitalis for one month resulted disastrously.

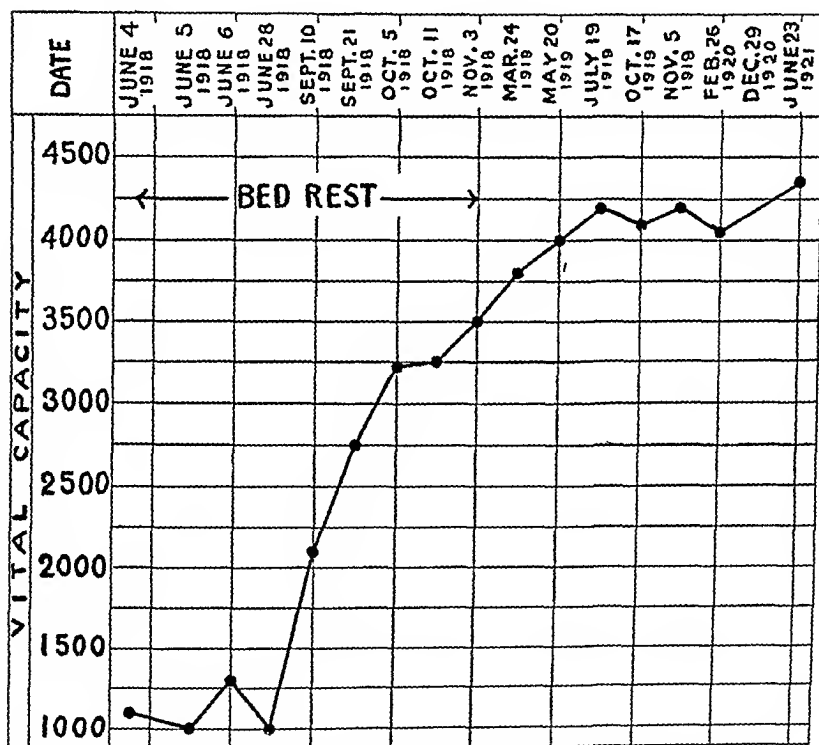


CHART IV. Case II.—Acute myocarditis. Increase of vital capacity from 23 per cent to 74 per cent while in bed.

CASE II.—The clinical history of this case has already been published, and a portion of the vital capacity readings.<sup>10</sup> The patient, a young man of twenty-one, had acute rheumatic myocarditis. He had been ill nearly three months when admitted to the Baptist Hospital, Boston, on June 4, 1918. For five weeks previous to entrance he had been unable to lie down in bed owing to

<sup>10</sup> Pratt, J. H.: Southern Med. Jour., 1920, 13, 481-490.

dyspnea. His vital capacity on admission was reduced to 1100 cc which was 23 per cent of the normal (West's standard). The next day it was 1000 cc or 21 per cent. After he had been at rest in the hospital twenty-four days the vital capacity was still 21 per cent. In September and October there was a marked rise. It increased from 45 per cent on September 10 to 69 per cent on October 11, being an increase of 1125 cc. When he left the hospital on November 3, the vital capacity was 74 per cent. Under rest and graduated exercise it rose slowly until it reached 89 per cent in July, 1919. He was then not short of breath after walking any distance on the level. He took up his work as a clerk in an importing house at this time. Two years later in June, 1921 his vital capacity reached the maximum. It was 4350 cc or 92 per cent of his normal. The chart (Chart IV) covers a period of three years and shows, (1) how low the vital capacity may fall in acute myocarditis and yet recovery occurs, (2) the beneficial effect of long continued rest in restoring the vital capacity, (3) the restitution of the vital capacity nearly to normal in the course of three years. This patient has an enlarged heart with aortic and mitral insufficiency.

CASE III.—The chart (Chart V) gives the vital capacity record over a period of five years, in this case of mitral stenosis with auricular fibrillation. Miss H. P. was forty-nine years of age in 1917, when the vital capacity was first determined. It was then 1600 cc or 52 per cent of the normal. She had pounding of the heart and a slight sense of suffocation and pressure across the sternum if she took even a few steps rapidly. At times when nervous she had these symptoms while at rest. In 1918 she was stronger. On May 29, I noted: "No trouble from heart. Possibly slight breathlessness at times. No palpitation." Her pulse that day was 46 at the apex and the wrist. The vital capacity was 2000 cc which was 65 per cent of her normal. Since 1918 she has been unable to move about freely without discomfort. The cardiac power has been less and the chart shows that the vital capacity has never been so high. Since June, 1919, it has only twice been recorded above 50 per cent.

In the late fall of 1920 she had a severe attack of rheumatic myositis, pericarditis and pleurisy. The great fall in vital capacity with its subsequent slow rise is indicative of involvement of the heart muscle by the rheumatic infection. On January 28, the vital capacity reading was only 350 cc or 11 per cent. The following day after the withdrawal of 990 cc of a somewhat turbid serous fluid from the left pleural cavity it was 500 cc or 16 per cent. The dyspnea which had been marked for several days was lessened. Two days later she appeared very sick and weak. An attempt to obtain the vital capacity was unsatisfactory. The amount of air expelled from the lungs was only 150 cc. It is probable that not

only this low reading, but the others obtained while the patient was very ill were less than the true vital capacity. The rise in the curve was slow and was only 925 cc or 30 per cent on March 16 when patient's general condition was much improved. The vital capacity rose until July, 1921, when it reached 1625 cc or 53 per cent. She could then walk slowly twenty-five to fifty yards on the level without breathlessness. In April, 1922, she was unable to lift light objects such as a blanket without producing pounding of the heart and a slight sense of suffocation. The vital capacity on April 18, 1922, was 1250 cc or 41 per cent. (On June 22, it had fallen to 1100 cc or 36 per cent without any definite change in her clinical condition.) The pulse has been kept slow during the past six years by the constant administration of digitalis.

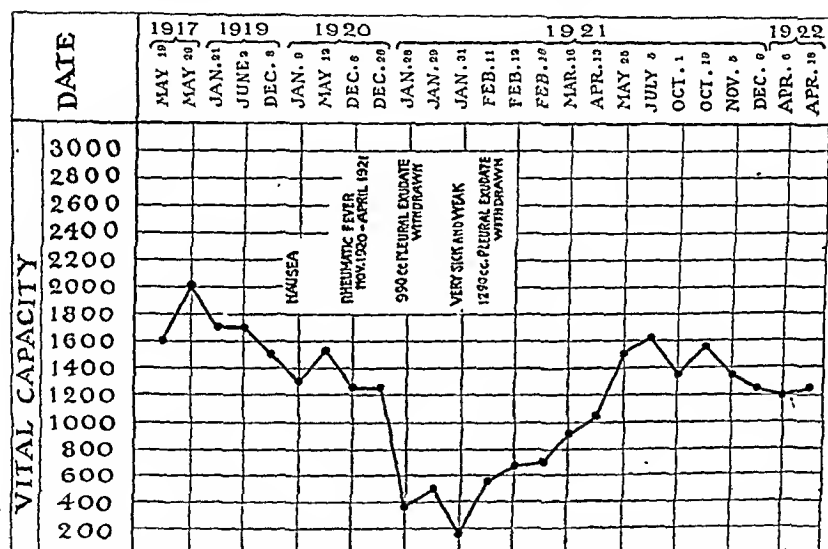


CHART V. Case III.—Vital capacity record over period of five years in a case of severe mitral stenosis. Fall of vital capacity during attack of acute rheumatic pericarditis with slow rise during convalescence.

CASE IV.—F. S., male, aged fifty years, when he came under observation in 1920. For ten months had been troubled with "wheezing" when he laid down at night. Increasing breathlessness on exertion gradually developed. About May, 1920, the effort of walking up a single flight of stairs made him short of breath. In June he had a severe attack of dyspnea which lasted all night. Cheyne-Stokes breathing first noticed then. It occurred every night when asleep. When I saw him he presented evidence of cardiosclerosis. The blood-pressure was high. Systolic pressure 180 mm.; diastolic pressure 120 mm. The pulse was regular, but alternating. His vital capacity was 2475 cc or 51 per cent of the

normal. He was admitted to the Baptist Hospital that day. Under strict bed rest and the Karrel diet the attacks of dyspnea ceased and the vital capacity rose to 3400 cc or 69 per cent on September 28. The administration of 2 grams of digitalis leaf in a single dose was followed by a second and more rapid rise (Chart VI). From October 9 to 11 the vital capacity increased from 3350 cc to 3650 cc. When he left the hospital on October 20, it was 3750 or 76 per cent of the normal. This was an increase of 1275 cc or 21 per cent during the six weeks of hospital treatment. On March 30, 1921, the auricles began to fibrillate. This proved to be a permanent arrhythmia. His heart was digitalized at the time of onset. The pulse remained slow, the rate being 60 to the minute.

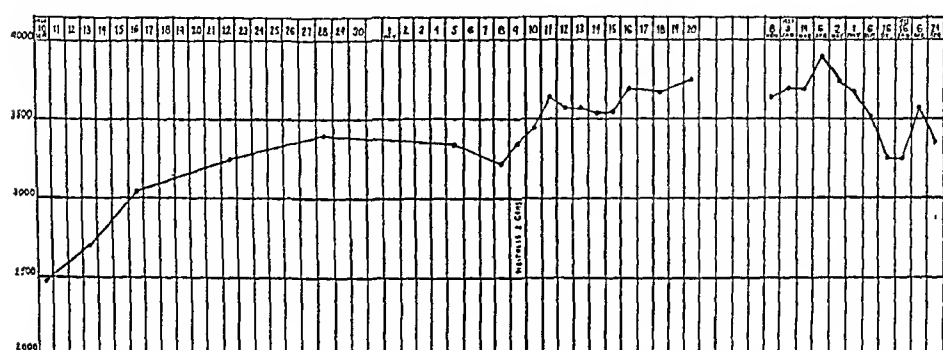


CHART VI. Case IV.—Cardiosclerosis with cardiac insufficiency. Vital capacity record from September, 1920, to April, 1922. Note rise as result of rest treatment followed by a second sharper rise after administration of digitalis. Slow fall in 1921 resulting from increasing cardiac weakness.

Four days later his vital capacity was taken and found to be higher than at any time since he had been under observation. It was 3875 cc or 79 per cent. On April 6, it rose to 80 per cent. With the onset of the abnormal cardiac mechanism, however, Cheyne-Stokes breathing which had disappeared when the patient's condition improved in the hospital, returned and persisted. There was a gradual fall of vital capacity from the height of 80 per cent reached in April, 1921 to 66 per cent in December. In February, 1922, he began to be troubled again with dyspnea when at rest. His sleep was troubled. He would awake during the hyperpnoeic phase of Cheyne-Stokes breathing. Readmitted to the Baptist Hospital. Under the usual treatment, by rest, morphin, digitalis, and Karrel diet, his condition improved and the vital capacity rose to 3575 cc or 73 per cent on April 6.

In this case four points may be emphasized. (1) The steady slow rise of the vital capacity after rest treatment was begun in September 1920, lasting eighteen days, then a stationary condition for a week followed by a slight drop. (2) The sharp sudden secondary rise beginning October 9, 1920, which is attributed to digitalis. (3) The

rise to the maximum on April 6, 1921, after the establishment of the abnormal cardiac mechanism (auricular fibrillation). (4) The slow steady fall from April to December, 1921, accompanied for several months by only slight signs of diminishing cardiac power.

The graphic records on the charts of these and similar cases show the value of long continued observations of the vital capacity repeated over a long period of time in measuring the increase or decrease of cardiac power. They will be found to be a distinct aid in the treatment and prognosis of heart disease.

**Conclusion.** I am sure of the facts presented. The deductions given are simply my interpretation of them. I would present this work in the same spirit that moved John Hutchinson in 1846 to close the report of his studies with these words. "The deductions I have ventured to draw" (from the facts presented) "I wish to advance with modesty, because, time, with its mutations, may so unfold science as to crush these deductions and demonstrate them as unsound. Nevertheless, the facts themselves can never alter, nor deviate in their bearing upon respiration—one of the most important functions in the animal economy."

---

### EXPERIENCES IN NEW YORK HOSPITAL WITH THE TREATMENT OF LOBAR PNEUMONIA BY A SERUM-FREE SOLUTION OF PNEUMOCOCCUS ANTIBODIES.\*

BY LEWIS A. CONNER, M.D.,

NEW YORK.

DURING the past two years all the cases of lobar pneumonia admitted to the adult wards of the First Medical Division of the New York Hospital have been treated by the intravenous use of a serum-free solution of pneumococcus antibodies prepared according to the method of F. M. Huntoon<sup>1</sup> and supplied to the hospital by the Mulford Biological Laboratories. The study of the effects of this antibody solution has been made with the coöperation with the Second Medical Division of Bellevue Hospital where the same method of treatment has been employed during the same period of time.<sup>2</sup>

The preparation of the solution is based upon the capacity of

\* Read at the meeting of the Association of American Physicians, Washington, D. C., May, 1922.

<sup>1</sup> Tr. Philadelphia Path. Soc., 1920, 22, 75. Jour. Immunol., 1921, 6, 117. Huntoon and Etris: Jour. Immunol., 1921, 6, 123. Huntoon and Craig: Jour. Immunol., 1921, 6, 235.

<sup>2</sup> Ceeil and Larsen: Jour. Am. Med. Assn., 1922, 79, 343.

bacteria to absorb their specific antibodies from immune serum. Pneumococci of the three fixed types are exposed to the action of a polyvalent immune serum. The organisms are then centrifugated out and washed to remove the serum proteins. These sensitized bacteria are then treated with a mildly alkaline salt solution in which some of the attached antibody splits off and becomes free. It is this solution containing the freed antibodies which, after some further treatment and standardization, is used therapeutically. The solution contains 0.85 per cent of sodium chloride, 0.25 per cent of sodium bicarbonate and a small amount of bacterial proteins. The serum proteins remaining are too small in amount to detect by chemical means. The solution in test shows antibodies against all three fixed types of pneumococci although its potency is much greater against Type I than against the other two types.

In view of the fact that the medical service is a comparatively small one it was thought best to subject all the pneumonia patients to this method of treatment rather than to attempt to run simultaneously a series of control cases, and, in order that the mortality figures under this method of treatment might fairly be compared with those of the hospital in other years, all cases not frankly convalescent, even those with an obviously hopeless outlook, were included in the treatment. The experiment was carried over two winter seasons in order to lessen somewhat the chance of error due to seasonal variation in the severity of the disease, and the treatment was limited to adult cases because of the much more favorable course that the disease is known to run in children.

Among the 120 cases in adults diagnosticated as lobar pneumonia only 4 failed to receive treatment by the antibody solution. One of these 4 was admitted in coma, with pulmonary edema, and the diagnosis was established only by autopsy. The 3 other cases failed to receive the treatment either because they were convalescent when admitted or because the solution was not available at the time. These all recovered.

In addition to the use of the antibody solution the patients received the usual symptomatic treatment. Digitalis was administered only to such patients as seemed to demand special cardiac support.

The routine practice has been to give the first intravenous injection of the solution just as soon as the diagnosis could be definitely established, without waiting for the report of the sputum typing, and to repeat the injection daily thereafter until the temperature showed no further disposition to rise materially or until it was obvious from other indications that the patient was out of danger. One patient received 9 injections, several received 6, a majority of the patients received either 2 or 3 and 34 patients were given but a single dose. After some experimentation the routine dosage decided upon was 50 cc of the solution for men and 25 cc for



women. Occasionally smaller doses were given when the general condition of the patient seemed to demand caution.

The immediate effects of the injection are very similar to those frequently seen, especially in febrile cases, after the intravenous injection of any foreign protein. After an interval varying from twenty-five to forty-five minutes there is usually a sharp rigor lasting from twenty to thirty minutes, with a rapid rise of temperature of from 2° to 4°. Temperatures of 106° or 107° F. are not very uncommon. During the chill the pulse becomes rapid and small, the color dusky and cyanotic and, if the reaction is severe, there may be a transient mild delirium. The rise of temperature is promptly followed by a sharp drop which in the course of a few hours may amount to 6° or 7°. This fall in temperature is usually accompanied by profuse sweating, marked slowing of the pulse and a striking improvement in all the subjective symptoms.

In favorable cases this drop in temperature may mark the end of the febrile stage and the beginning of convalescence. In most cases however the fever begins to rise again within twelve hours and within twenty-four hours may reach its former level. Very often, however, the temperature does not go quite so high and the patient's general condition will have changed so much for the better that a second injection may seem unnecessary. The response to a second injection is usually quite similar to that to the first. Occasionally the reaction is less pronounced, and in a few instances a second or a third injection has been followed by a more severe reaction than the first. Rarely a case is met with in which no distinct reaction occurs and no fall of temperature results.

Among the 116 patients treated the infecting bacterium was identified in all but 13 instances. Among these 103 cases in which the exciting organism was known, were 13 in which the bacterium incriminated was *not* the pneumococcus. In 9 of these latter a hemolytic streptococcus was found, in 1 a non-hemolytic streptococcus and in the remaining 3 the Friedländer bacillus.

TABLE I.—MORTALITY OF ALL PNEUMONIA CASES TREATED, AND OF THOSE TREATED CASES WHICH PROVED TO BE DUE TO ORGANISMS OTHER THAN THE PNEUMOCOCCUS.

	Total cases treated.			Non-pneumococcus cases treated		
	Cases.	Died.	Mortality.	Cases.	Died.	Mortality.
1920-21	76	10	13.1%	8	3	37.5%
1921-22	40	7	17.5%	5	3	60.0%
Total 2 years	116	17	14.6%	13	6	46.1%

In Table I is shown the total number of patients treated in each of the two seasons, with the percentage mortality, and also the mortality figures among the patients caused by organisms other than the pneumococcus. It will be seen that for the 116 patients representing the entire number treated the mortality was 14.6 per cent. Among the 13 non-pneumococcus patients however the death rate was 46.1 per cent.

In 13 of the cases, as has been said, the exciting microörganism could not be identified, because of inability to secure satisfactory sputum for typing and of the fact that blood cultures were sterile. As the mortality in this group was very low (7.7 per cent) it seems highly probable, however, that they were all pneumococcus cases and they have been reckoned as such in Table II, in which the figures for 103 pneumococcus cases are given.

TABLE II.—MORTALITY OF PNEUMOCOCCUS CASES.

	Proved pneumococcus cases.			Probable pneumococcus cases.			Total pneumococcus cases.		
	Cases.	Died.	Mortality.	Cases.	Died.	Mortality.	Cases.	Died.	Mortality.
1920-21	58	6	10.3%	10	1	10.0	68	7	10.3%
1921-22	32	4	12.5%	3	0	0	35	4	11.4%
Total 2 years	90	10	11.1%	13	1	7.7	103	11	10.6%

Table III shows the relative proportion of the different types among the 90 proved pneumococcus cases, together with their respective death rates. Type IV is conspicuous by reason both of its high incidence and its very low mortality.

TABLE III.—TYPES OF PNEUMOCOCCUS. ANALYSIS OF 90 CASES.

Types.	Cases.	Percentage of total.	Died.	Percentage mortality.
I	23	25.5	3	13.0
II	9	10.0	2	22.2
III	9	10.0	3	33.3
IV	49	54.4	2	4.1

In Table IV is shown the number of pneumococcus cases yielding positive blood cultures and the fate of these cases. It should be

explained that as a rule only a single blood culture was taken. It is possible that more frequent cultures might have shown a somewhat higher ratio of bacteriemias.

TABLE IV.—FATE OF PNEUMOCOCCUS CASES WITH POSITIVE BLOOD CULTURES.

Types.	I.	II.	III.	IV.
Recovered	7	1	0	2
Died	2	2	0	0
Total	9	3	0	2

**BEHAVIOR OF THE LEUKOCYTES.** The effect of the antibody injections upon the leukocytes was studied in a number of the cases, with extraordinarily varying results. In a majority of these cases there was either a slight, transient diminution in the number of leukocytes and in the percentage of polymorphonuclear cells or no change at all. In some cases the reduction in the number of leukocytes was considerable and seemed to be permanent, while in a few, profound changes in the leukocytes were observed. For example, in one patient, who on admission showed a leukocytosis of 21,800 and a polymorphonuclear percentage of 89, the count, thirty minutes after the first injection and at the beginning of the chill, was 5100 and the polymorphonuclear cells were 90 per cent; thirty minutes later, at the end of the chill, the leukocytes numbered only 1500 and the percentage of polymorphonuclear cells was 40; forty minutes later the count was 3750 and 90 per cent, with many transitional cells; four hours later the leukocytes numbered 18,000 with 91 per cent of polymorphonuclears and many transitionals, and twelve hours later the leukocytes had again fallen to 4000 with 77 per cent of polymorphonuclears. In only a very few cases was an increase in the leukocytes observed and in these the change was slight and insignificant. It seems safe to conclude therefore that whatever the nature of the action of the antibody solution the beneficial effects cannot be ascribed to any stimulation of the phagocytic leukocytes.

**EFFECT UPON RESOLUTION.** In those cases in which the effect of the treatment was sufficiently early and decisive to give value to the observations it was found, as was to have been expected, that no such prompt and striking effects were produced upon the anatomical changes in the lungs as were seen in the constitutional manifestations of the disease. Evidences of the beginning of resolution usually appeared within twenty-four or forty-eight hours after the critical defervescence but the process seemed rather more deliber-

ate than after a normal crisis. Nevertheless in a good many cases one had the impression that both defervescence and the completion of resolution had been hastened by the treatment.

COMPLICATIONS. The series of cases studied was too limited to enable one to draw any satisfactory conclusions as to the effect of the treatment on the tendency to complications. Among the 103 pneumococcus cases empyema occurred 6 times (Type I, 2 cases; Type III, 1 case; Type IV, 3 cases) and pericarditis 3 times (Type II, 1 case; Type IV, 2 cases).

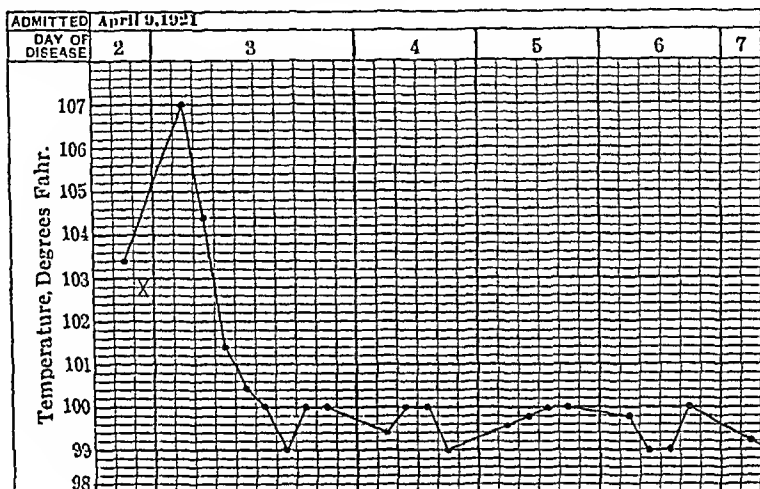


CHART I

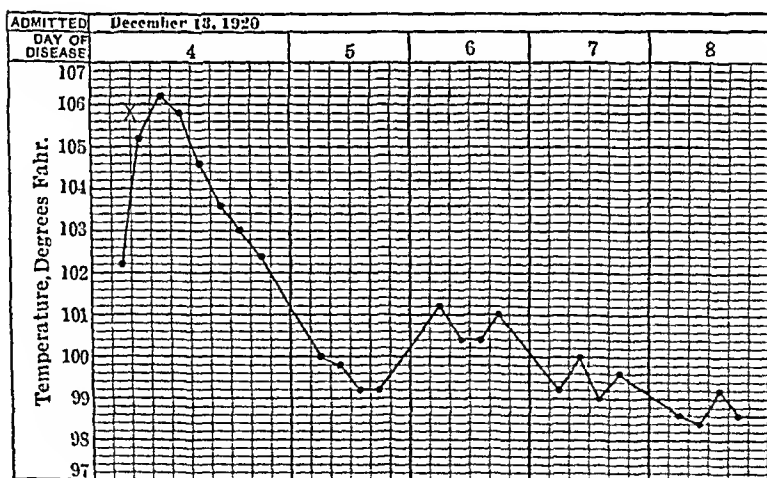


CHART II

**Discussion.** In attempting to estimate the effectiveness of any form of treatment in lobar pneumonia one must rely chiefly upon the influence of such treatment upon the death rate. There are, however, two other eriteria which are entitled to some weight; namely, the ability of the treatment to eut short the disease when

## CONNER: TREATMENT OF LOBAR PNEUMONIA

administered early, and the results of treatment in cases associated with a demonstrable bacteriemia.

In the present series we have unfortunately no group of control cases carried on simultaneously with which to compare the mortality

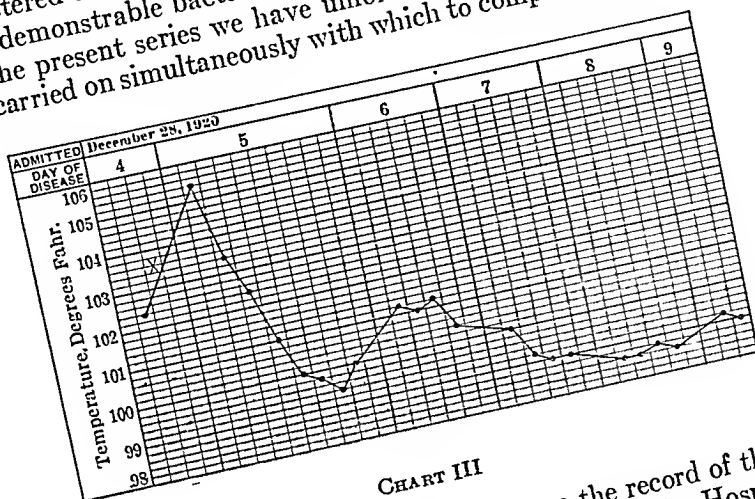


CHART III

rate of the treated cases, and must rely upon the record of the Hospital in past years. Taking the official figures of the Hospital for the last twenty years for which these are available up to and including 1917 (the years 1918 and 1919 having been influenza years) it is found that with the exception of three years the mortality of lobar pneumonia ranged constantly between 30 and 39 per cent. In the

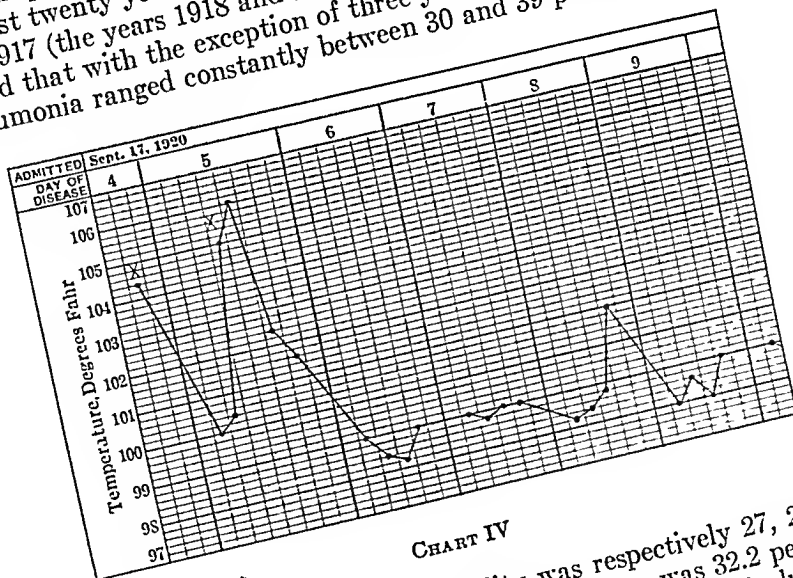


CHART IV

three exceptional years the mortality was respectively 27, 26 and 20 per cent. The average for the twenty years was 32.2 per cent. It should be emphasized, however, that these figures include not only the adult cases but also all those occurring in children, in whom

the death rate from lobar pneumonia is, of course, very much lower. The cases of pneumonia in children constitute from 20 to 30 per cent of the total Hospital cases, so that the mortality figures for the adult cases alone would be considerably higher than those given

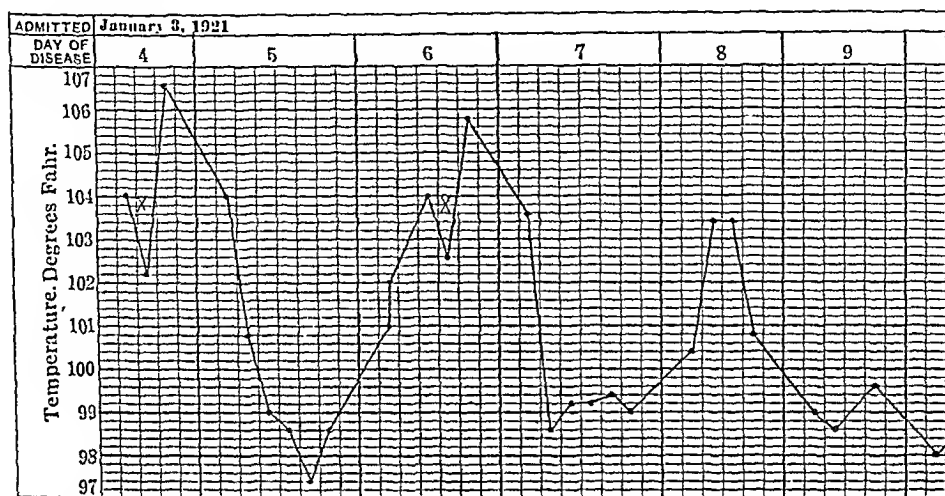


CHART V

above. In contrast to these hospital figures we have for the period between July, 1920 and April 20, 1922, 116 treated patients, with a mortality of 14.6 per cent, or if we include the 4 patients not treated with the antibody solution, 120 patients with a mortality of 15 per cent. One must assume then either that in these two last years the pneumonia cases ran a much milder course than that of

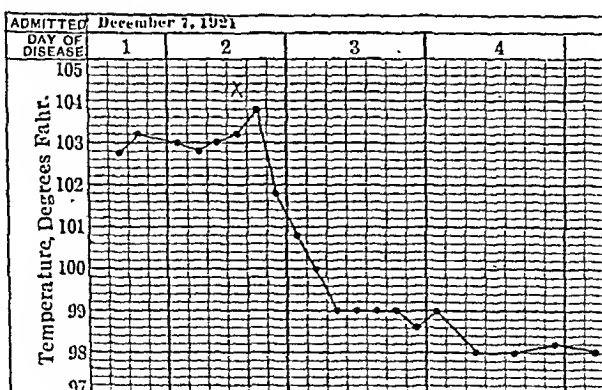


CHART VI

other years or that the special treatment had a distinct effect in reducing the mortality. As to the former assumption there are certain facts which seem to indicate that the disease may have been somewhat milder than usual. These are the high incidence of

Type IV cases, amounting to 54 per cent of the proved pneumococcus cases, and the small percentage of positive blood cultures found among this group. On the other hand the impression one received from the appearance and condition of the cases upon admission was that they were quite of average severity. In respect of their degree

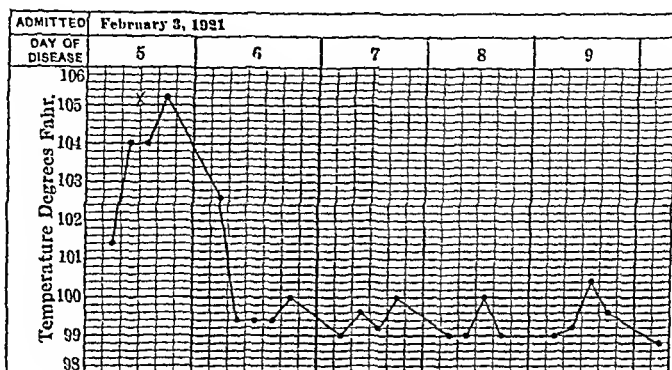


CHART VII

of constitutional disturbance and of the extent of lung involvement they gave no indication of being especially mild cases.

If we exclude from the 116 treated cases the 13 known to have been due to organisms other than the pneumococcus, in which no

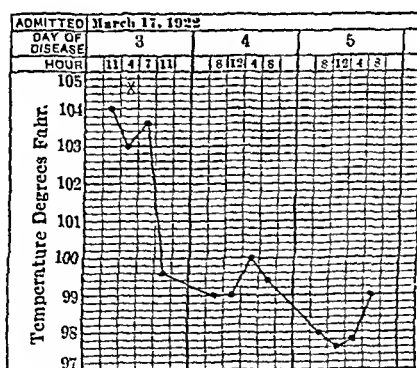


CHART VIII

effect from the treatment could reasonably be expected, we have 103 cases with a mortality of 10.6 per cent.

From statistics collected by Cole<sup>3</sup> from all available sources he concludes "that when the disease is not influenced by specific

<sup>3</sup> Article on Lobar Pneumonia, Nelson *Loose-leaf Medicine*, vol. 1, p. 203.

treatment the average hospital mortality rate in cases associated with the different types of pneumococci is about as follows:

	Mortality rate.
Cases associated with Type I pneumococci . . .	25 to 30 per cent.
Cases associated with Type II pneumococci . . .	25 to 20 "
Cases associated with Type III pneumococci . . .	45 to 50 "
Cases associated with Type IV pneumococci . . .	15 to 20 " "

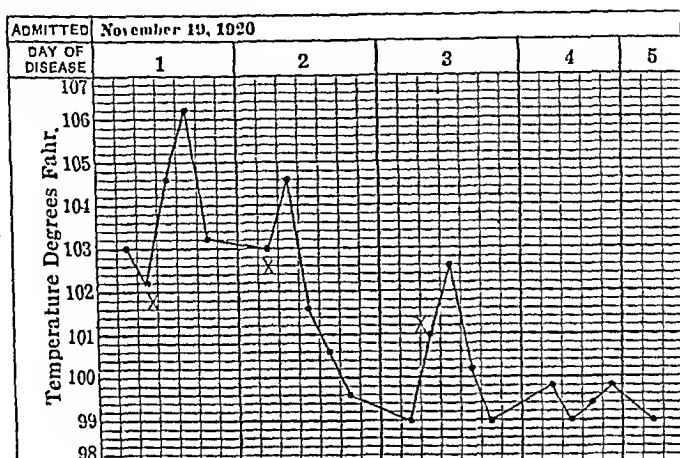


CHART IX

Among the 90 proved pneumococcus cases in the present series the mortality rate in each of the four types was respectively 13.0, 22.2, 33.3 and 4.1 per cent. The number of the cases of Types II and III is too small to be of much value statistically, but there is nothing

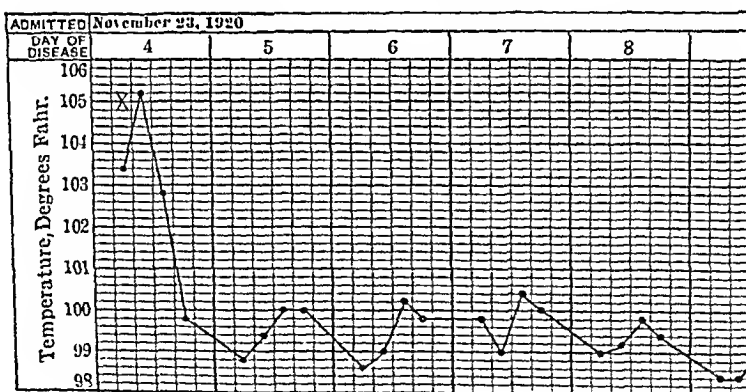


CHART X

in the mortality figures to suggest that the treatment had any special influence upon these cases. With respect to Types I and IV however, the percentage mortality is so much below that of the averages for these types that it is difficult to resist the conviction that the treatment did actually have a favorable influence upon the death rate.



The question whether or not the treatment by the antibody solution is capable of cutting short the disease is one that is difficult to answer positively, for one can never be certain in a given case that the crisis may not occur spontaneously as early as the third or fourth day of the disease. Such early crises are seen in a small percentage of the cases under any form of treatment. Nevertheless in the present series, when the opportunity was afforded of using the treatment in the early days of the disease, a permanent fall of temperature followed immediately after the injection in such a considerable proportion of the cases that one can hardly escape the conclusion that in these cases the early defervescence was the direct result of the treatment.

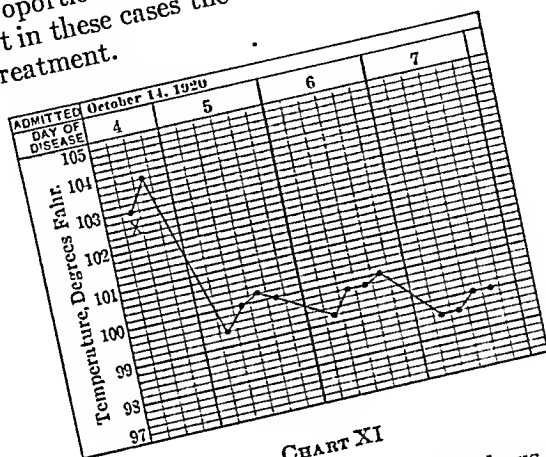


CHART XI

In the series of temperature charts which follows some of the more striking examples of such early defervescence are shown. A similar immediate and permanent fall in temperature was seen also in some of the cases admitted in a later stage of the disease, but in such cases the likelihood is much greater that this critical drop may have been merely a coincidence.

In the charts shown the type of pneumococcus found in the sputum is indicated in the upper right corner. The crosses (X) mark the points at which an injection was given. Although examples of such early defervescence are shown in cases associated with each of the four pneumococcus types, it will be noted that some of the most striking effects were obtained in Type IV cases. This result was entirely unexpected and is difficult to explain. It is hardly necessary to say that the temperature charts presented are not intended to represent the effect of the treatment in the average case. A good many cases, even among those that received fairly early treatment, failed to show such prompt and convincing results.

The number of pneumococcus cases with positive blood cultures is too small to be entitled to much weight in attempting to estimate the effectiveness of the treatment. Among the 14 cases, however,

10 recovered. This mortality rate of 28.5 per cent is considerably less than that expected under the ordinary form of symptomatic treatment. In Cole's series of cases at the Hospital of the Rockefeller Institute there were (excluding Type I cases in which specific treatment was employed) 199 cases in which blood cultures were positive, and among these the death rate was 67.1 per cent.<sup>4</sup>

NATURE OF THE THERAPEUTIC EFFECTS. If, from the evidence offered above, it be assumed then that the special treatment employed in this series of cases does actually possess some curative qualities in lobar pneumonia the question at once arises as to what the nature of these curative qualities is. Are the effects the result solely of the content of the solution in antibodies of the three fixed types of pneumococci; or does the solution, in addition to the specific antibodies, contain perhaps some group protective bodies of less specific nature, or finally, are the effects entirely non-specific and of allied nature to those frequently seen after the intravenous injection of any foreign protein?

It is difficult to ascribe the results observed in the present series of cases solely to the presence in the solution of antibodies of the three fixed types for the reason that some of the most striking effects were seen in cases associated with Type IV pneumococci. Not only was the mortality rate among this group of cases extremely low (4.1 per cent) but some of the most convincing evidence as to the ability of the treatment, in certain cases at least, to abort the disease is found among Type IV cases.

The theory that the action may be purely non-specific, and due merely to the injection of a foreign protein, gains a certain plausibility from the fact that the constitutional reaction immediately following the injection, which appears to be an essential part of the curative mechanism, is indistinguishable from that usually seen after injections of protein, and from the fact also that the therapeutic effects seem to be quite as distinct in the Type IV cases as in those of the fixed types. Such non-specific action cannot well be explained upon the basis of increased phagocytosis for in most cases there was a fall, rather than a rise, in the leukocytes as a result of the injections.

Among several other theories advanced to explain the beneficial effects frequently seen in various infectious processes following the intravenous injection of foreign protein substances is that which ascribes to such non-specific injection the power of mobilizing specific antibodies which have already been formed but have not been detached from the tissue cells. Ludke and others have offered experimental evidence which indicates that protein injections do increase the amount of circulating antibodies in immune animals. Recently Larson,<sup>5</sup> as the result of experimental work, has suggested

<sup>4</sup> Cole: *Loc. cit.*

<sup>5</sup> *Minnesota Medicine*, 1919, 2, 332.

that many bacteria, such as streptococci, pneumococci, etc., are imperfect antigens in that, while they are capable of producing antibodies, they lack the power of setting free these antibodies from the tissue cells, and that this latter effect can be brought about by foreign protein injections. In other words, Larson believes, the stimulus necessary to excite the cells to the production of the antibodies is specific but that needed to cause the cells to throw off the antibodies—the exfoliative stimulus—is not necessarily specific. In accordance with this theory one might assume that the effects observed in the present series were due not so much to the specific antibodies contained in the solution as to the antibodies liberated from the patient's own cells by some non-specific action (protein or otherwise) of the injections.

But there are several difficulties in the way of accepting the theory of purely non-specific action. Apart from the fact that the solution is known to contain only minute quantities of protein (since practically all of the serum proteins have been removed by washing), there is the striking difference in its action upon the pneumococcus pneumonias and upon those due to the streptococcus and Friedländer's bacillus. Among the 13 patients associated with these latter organisms the mortality rate was 46.1 per cent, and there was nothing in the clinical course of any of the cases to suggest that it has been influenced favorably by the treatment. Finally, there is the objection that although foreign protein injections have often been used in lobar pneumonia the results have been generally disappointing. Petersen,<sup>6</sup> upon theoretical grounds, is inclined to believe that little can be expected in pneumonia from this form of therapy.

The hypothesis that the solution may contain beside the specific type antibodies some group protective substances of less specific nature would seem, perhaps, best to explain the results observed, but until much further evidence is secured the nature of the therapeutic action of this method of treatment must remain in doubt.

**ADVANTAGES AND DRAWBACKS OF THE METHOD.** It is clear that any method of treatment which permits of the introduction into the circulation of the specific pneumococcus antibodies in a serum-free solution has, *a priori*, certain obvious advantages over the methods of rational therapy in present use. The possible risk of anaphylactic shock and the serious discomforts of serum sickness are entirely avoided. Moreover the fact that treatment need not be withheld until sputum typing has been done and the causative organism definitely determined means a saving of from twelve to twenty-four or more hours—a point of no inconsiderable importance, since time is a factor to be reckoned with.

The treatment under consideration certainly possesses these

<sup>6</sup> Protein Therapy and Non-specific Resistance, New York, 1922, p. 125.

advantages. In none of the cases treated was there any suggestion of an anaphylactic reaction or of subsequent serum sickness. Moreover the quantity of liquid to be injected is relatively small and the technic simple. The method has, however, one serious drawback in that the immediate, or so-called thermal, reaction is sometimes very severe and may even result in death. In one of the present series of cases death seemed to be directly due to the severity of this reaction. A previously healthy man, aged thirty-six years, admitted on the evening of his third day of illness, showed suspicious signs in his right upper lobe, with evidences of very severe intoxication—rapid pulse, great prostration and mild delirium. The following morning there were frank signs of consolidation and he was given an intravenous injection of 50 cc of the antibody solution, the routine dose for male patients. Thirty minutes later he had a severe rigor. His temperature rose rapidly to 109° F., he became unconscious and cyanotic, with involuntary stools, extremely rapid, feeble pulse, labored breathing and profuse sweating. The hyperpyrexia continued for four hours, when death ensued. No sputum was obtained for typing but a postmortem lung puncture yielded a growth of non-hemolytic streptococcus. Although this was the only fatality that could in any way be ascribed to the treatment the reaction in several other cases was for the moment distinctly alarming. It was the occurrence of these severe thermal reactions that forced the decision to limit the dosage in women to 25 cc. Even this amount occasionally produced a severe reaction. Indeed there seemed to be no very distinct quantitative relationship between the amount of the solution injected and the severity of the thermal reaction. In one individual 25 cc or even 10 cc might produce a more severe immediate effect than would 50 cc in another, and even in the same patient the injection of 50 cc might cause no greater reaction than would 25 cc.

The question as to whether this thermal reaction is an essential part of the therapeutic mechanism could not be definitely answered. The general impression has been that the beneficial effects were apt to be more distinct in cases which responded with a sharp thermal reaction, and yet in a few instances a prompt and permanent drop in temperature was seen when the injection was followed by no chill and by no distinct rise in fever.

As a result of our two years of experience with the use of this method of treatment I feel that the evidence that it has some actual curative value is too strong to be disregarded. This evidence relates chiefly, though not entirely, to cases associated with Type I and Type IV pneumococci. If the therapeutic effects depend altogether upon the specific, type antibodies contained in the solution one must then assume that the antibodies of one or more of these types are effective in neutralizing the toxic products generated by at least certain of the organisms comprising the heterogeneous

group known as Type IV. Aside from the theoretical importance of Huntoon's work in obtaining antibodies free from immune serum, the method seems to me to mark a step forward along the path toward a satisfactory form of rational treatment for lobar pneumonia. That this method at present constitutes such a satisfactory form of treatment cannot be asserted. Much further clinical study is needed and some means must be found of controlling the severity of the immediate reactions before it can safely come into general use.

**Summary.** The effect of treatment by the intravenous injection of a serum-free solution of antibodies of the three fixed types of pneumococci was studied in a series of 116 cases of lobar pneumonia in adults, covering a period of two years. All patients admitted to the service were treated, without any attempt at selection. The death rate for these 116 patients was 14.6 per cent. Among this group of cases were 13 in which the exciting organism was shown to be a streptococcus or the Friedländer bacillus. The mortality rate for these patients was 46.1 per cent. Of the remaining 103 cases 90 were proved to be due to the pneumococcus and the others, because of the low death rate among them, were regarded as probable pneumococcus cases. For these 103 patients the death rate was 10.6 per cent. Among the 90 proved pneumococcus cases Type IV pneumonias were conspicuous both by their high incidence (54.4 per cent) and by their very low mortality (4.1 per cent). Although the series of cases studied is too small to justify any positive conclusions the figures suggest that the treatment had some real curative value, with respect to Type I and Type II cases at least, and this impression is supported by the fact that in a considerable proportion of the cases in which treatment could be instituted early the progress of the disease was stopped short, and by the further fact that recoveries among the cases associated with positive blood cultures were more frequent than is usual under ordinary methods of treatment. The nature of the therapeutic effects of the solution is obscure in view of the apparent effectiveness of the treatment in Type IV cases. It is difficult to ascribe these solely to the contained type antibodies unless it be assumed that some of these may be effective against certain of the organisms of Type IV. The difficulties in the way of explaining the beneficial results of the treatment on the score of some purely non-specific action are discussed. The method is free from the disadvantages incident to the injection of large amounts of serum. It has, however, one serious defect in that the immediate reactions following the injections are often severe and are occasionally dangerous. In one patient death seemed to be directly traceable to the severity of this reaction. The method is believed to represent a step forward in the direction of a satisfactory form of rational treatment but further clinical study is needed and some means of controlling the severity of the immediate reactions to the injections must be found before it can safely be introduced into general use.

## PREGNANCY COMPLICATING HEART DISEASE.\*

BY HAROLD E. B. PARDEE, M.D.,

ASSISTANT ATTENDING PHYSICIAN NEW YORK HOSPITAL, CONSULTANT IN CARDIAC DISEASE, LYING IN HOSPITAL, NEW YORK CITY.

THE question of the effect of pregnancy upon patients with heart disease has had my special attention now for over two years. I was attracted to it by the fact that the mortality which has been presented by the obstetricians who have written on this subject was so remarkably great, varying from 25 per cent to 50 per cent in different reports. These reports it is true were concerned only with the patients who developed symptoms or signs of cardiac failure and so did not give a proper picture of the mortality from heart disease during pregnancy and labor. They entirely left out of the picture the large number of patients who pass through this period without cardiac insufficiency in spite of having well developed valvular disease. Even in this special group of those showing evidence of cardiac insufficiency the mortality seemed much higher than it should be and so the management of these severe cases presented a very definite and pressing problem.

Besides this, one is often called upon to give an opinion as to whether or not a certain woman with heart disease should be allowed to undertake childbearing. This is a question which we find it most difficult to answer, because the criteria upon which a decision should be based have not yet been definitely laid down. Here then we were doing pioneer work. It was felt that if a careful record were kept of the patients' complaints together with a thorough examination of the heart and lungs, the filling of the arteries and veins and a test of the patient's exercise tolerance, it would give us information, which when considered in the light of the patient's further course should go far toward finding out what features will help us in the prognosis. We *should* be able to say with reasonable certainty whether or not the patient is liable to develop severe cardiac failure during pregnancy or labor, and whether or not she will be worse off in respect to her cardiac compensation after having had the child than if she had not had it.

We have encountered cardiac disease in about 1 per cent of the patients who have applied to the hospital, to date about 50 patients in all but for various reasons only 35 are included in this report. (See Table I). Of these 7 had mitral regurgitation as the chief valve lesion, 20 had mitral stenosis, 5 had aortic regurgitation while 3 had both mitral stenosis and aortic regurgitation, so that there were 23 stenosed mitral valves and 8 leaking aortic valves in the series.

\* Read before the Section on Obstetrics and Gynecology, New York State Medical Society, Albany, N. Y., April 20, 1922.

Marked enlargement of the heart was present in 6 patients, 4 of these having both aortic and mitral disease. Ten patients had moderate (more than slight) cardiac enlargement. One of these had aortic disease, 1 a simple mitral regurgitation and the other 8 mitral stenosis with or without regurgitation.

TABLE I.—ANALYSIS OF 35 CASES.

Valve lesion.	Cases.	Per cent.	Enlargement.	Cases.	Per cent.
Mitral regurgitation . . . .	7	20	Marked . . . . .	6	17
Mitral stenosis . . . . .	20	57	Moderate . . . . .	10	29
Aortic regurgitation . . . .	5	14	Slight or none . . . .	19	54
Mitral stenosis and aortic regurgitation . . . . .	3	9			

Evidences of cardiac failure were prominent in 15 of the patients of this series and 4 died of it. This more serious group included 9 with mitral stenosis as their chief valve lesion, 3 with aortic regurgitation and 3 with both of these lesions; 5 of these hearts showed marked enlargement and 4 moderate (more than slight) enlargement (Table II.)

TABLE II.—ANALYSIS OF 15 SEVERE CASES.

Valve lesion.	Cases.	Per cent.	Enlargement.	Cases.	Per cent.
Mitral stenosis . . . . .	9	60	Marked . . . . .	5	33
Aortic regurgitation . . . .	3	20	Moderate . . . . .	4	27
Mitral stenosis and aortic regurgitation . . . . .	3	20	Slight or none . . . .	6	40

Mitral stenosis is more frequent than aortic regurgitation in the serious group, but I do not feel that this indicates it to be a more serious lesion. Its occurrence in the serious group is 60 per cent and in the series as a whole 57 per cent while aortic regurgitation comprises 20 per cent of the serious group and 15 per cent of the series as a whole in each case practically the same percentage. Note though, that all 3 cases of combined aortic regurgitation and mitral stenosis appeared in the serious group. Moderate cardiac enlargement was present in 27 per cent of the serious cases and 29 per cent of the series as a whole, practically the same percentage, but marked enlargement was found in 33 per cent of the serious cases and in only 17 per cent of all cases.

The presence of marked cardiac enlargement and of combined aortic regurgitation and mitral stenosis seem then to be the only pathological conditions which have a determining influence upon the seriousness of the patients cardiac disease. They are the only lesion more frequent in the serious group than in the whole series. Yet patients with one of these conditions and even with both of

them have been observed to go through pregnancy and labor without alarming symptoms developing.

**Functional Grouping of Patients.** In a further attempt to solve the problem we have used a classification of these patients based upon an estimation of the functional condition of the heart. They were divided into four groups on a basis of the circumstances under which they complained of symptoms of cardiac failure (breathlessness, palpitation, etc.) and upon their observed reaction to a test exercise (swinging a 5 or 10 pound dumb-bell held in both hands 20 times from near the floor to over the head).

GROUP I includes those women who have definite physical signs of valvular disease and yet have never noticed unusual shortness of breath on exertion either before or during pregnancy. Their reaction to the test exercise was normal, or if not they were placed in Group II.

GROUP II includes in addition to these, women who with definite signs of valvular disease have never noticed unusual shortness of breath on exertion except during this pregnancy or a preceding one or on unusual exertions when not pregnant. Their reaction to the test exercise was normal or moderately increased. If it was markedly increased they were placed in Group III.

GROUP III includes besides these, women who have been kept conscious of their heart disease by the appearance of shortness of breath or palpitation on more than ordinary exertions when they were not pregnant, and whose symptoms have increased during this pregnancy or a preceding one but have not become severe enough to necessitate rest in bed, either during this pregnancy or at a time less than six months before its beginning. Their reaction to the test exercise was moderately increased: if markedly increased they were placed in Group IV.

GROUP IV includes besides these, women who have had symptoms of cardiac failure on moderate exertions when they were not pregnant or who have been in bed from cardiac failure within six months of the time of pregnancy. Their symptoms have become more easily produced during pregnancy but need not have made rest in bed necessary. Their reaction to the test exercise was moderately or markedly increased.

The results of using this grouping have been published in detail<sup>1</sup> and it seems to be of considerable value in helping to decide whether or not the patient will have severe cardiac failure during pregnancy or labor.

None of the 17 patients in Groups I and II developed marked symptoms of cardiac failure. Three of the 9 patients in Group III went through labor at full term without marked symptoms and 3 of the 9 patients in Group IV did the same. It was felt that 2

<sup>1</sup> Pardee: Jour. Am. Med. Assn., 1922, 78, 1188.



of these 3 Group IV patients owed their relatively good condition at labor only to the fact that the delivery was of the precipitate character so that the strain of labor was at a minimum.

It seems, then, that patients who fall into Groups III and IV comprise all or almost all (for our series of 35 is too small to allow us to draw very sweeping conclusions) of those who will later develop a serious degree of cardiac failure, and that the patients of Group IV are not likely to go through an average pregnancy and labor without trouble.

That some are able to go through without serious symptoms is due perhaps to features of the individual patient quite outside of the heart. During pregnancy some women are very active and cannot be restrained from doing a great deal while others are quite lethargic; moreover the reactions of the nervous system to the usual events of life will be very different from one patient to another. These things are an important feature of the management of a woman with failing compensation, for the over active or nervous woman will continually be throwing more strain on her heart than will one who is quiet and composed.

The strain of labor itself is very different in different patients also, and this is obviously of great importance from the point of view of heart failure. A quick easy delivery will be much less of a drain on the reserve powers of the heart than will a protracted and difficult one. Therefore a small pelvis or a large baby or a primiparous mother are matters which must be considered as carefully as the more special circulatory features of cardiac enlargement or valvular lesion.

**Treatment.** The management of patients with heart disease during pregnancy is vitally dependent upon these observations. It is evident that no matter what the valvular disease or the size of the heart, the patient is safe as long as she does not develop severe heart failure. Therefore abortion need never be advised on any grounds but those of the appearance of heart failure. Nor need we fear its sudden and unexpected appearance, for it is a very rare event for severe failure to appear suddenly without warning; we have seen it only once in 50 cases. Usually it comes on gradually over a period of several days or weeks. Occasionally it comes less gradually during the hours of labor, but practically always gradually so that when its onset is recognized we can take steps to ward it off before it is too late. Quickening of the pulse and an increase in the respiration are the first signs in any case, and along with these may go the finding of persistent rales at the bases of the lungs posteriorly which do not disappear with deep breathing. If these signs are disregarded the pulse and respiration become still quicker and edema of the lungs may appear with cyanosis and frothy sputum. Edema of the lungs may sometimes appear very abruptly in a patient who has previously shown some quickening of the pulse and respiration.

The secret of the successful treatment of these patients is to endeavor to prevent the appearance of pulmonary edema. During pregnancy when the pulse and respiration are constantly more rapid than normal and rales appear at the bases of the lungs the patients should receive the usual treatment for heart failure of this degree. They should be kept in bed on a light diet with restricted fluids and should be given a properly thorough course of digitalis for at least two weeks. If this does not relieve the dyspnea and diminish the rales in the lungs, and usually it will do so, then and not until then, do I feel that operative interference is indicated.

When interference is indicated in these patients, no matter whether during pregnancy or during labor, the operation is being performed for the purpose of relieving a strain on the heart which is trying it beyond the limit of its capabilities. It seems almost unnecessary to make this statement and yet I think that only by facing it squarely can we be brought to see what sort of operation is indicated and what sort contraindicated. The operation must be such a one that it relieves the strain upon the heart *promptly* and *must not itself impose an added strain*. If the cervix is not dilated the operation of choice seems to me without question to be the abdominal section. If the cervix is dilated and the head engaged, then forceps may suffice. I am not favorable to version and extraction for I feel that the shock of the intra-uterine manipulation is a factor to be avoided, so with a high disengaged head I would advise abdominal section even with some dilatation of the cervix. Ether is the anesthetic of choice and gas I think very dangerous even if given with oxygen, for it raises the blood-pressure and increases the work which the heart must do, thus throwing an added strain on the circulation.

Never operate during a period of severe cardiac failure. The risk is greater then than at any other time and I think greater with operation than without it. The added strain may be the decisive factor in causing death. We should aim to operate either before severe failure has set in or after it has been recovered from and thus deal with a heart whose reserve is not entirely used up.

When a patient has reached such a state of cardiac failure that treatment has necessitated rest in bed and when treatment has resulted in improving the compensation so that rales have disappeared from the lungs and perhaps the effort of walking on the level can be undertaken without undue shortness of breath, it is then time to consider what this patient's further course should be. How important is it that this baby should be born? How much chance with her own life does the mother wish to take?

Interference may be advisable but it is not obligatory for some cases go on very well even after an attack of severe decompensation and may, with proper care, complete their pregnancy and labor without further serious failure. Other cases though will relapse even with

the most careful treatment and these should have an abdominal section performed when the relapse is seen to be imminent. The severely ill patients should never be allowed to go beyond the fortieth week, for a large baby is, as has been pointed out, very undesirable. With patients who are considered to be of the most serious type, the Group IV cases, it seems to me that it would be well to consider inducing labor at the eighth month, thus ensuring a small child and an easy delivery, though this is less true with primipara than with multipara.

*Severe Cases.* Sometimes in hospital work patients are first seen during an attack of acute cardiac failure with edema of the lungs. They are markedly dyspneic, cyanotic, coughing up pinkish frothy sputum, and show a very rapid heart rate, 120 or over, distended veins in the neck and labored rapid respirations. If this woman is in labor and it cannot be quickly ended by a medium or low forceps operation her case is nearly hopeless. Even before the operation is attempted, though, the cardiac failure should be treated to, if possible, improve her chances of pulling through. A hypodermic of  $\frac{1}{4}$  grain of morphin sulphate along with  $\frac{1}{50}$  grain of atropin sulphate should be given at once. Phlebotomy should be done and continued until the distended neck veins are collapsed, removing from 5 to 10 or more ounces of blood if necessary to produce this effect. Digitoxin should be given intravenously in a dose of  $\frac{2}{100}$  grain.

This treatment will usually result in a temporary cessation of labor, an improvement in the respiratory distress and a diminution of the rales in the lungs. The patient should be carefully watched when labor shows signs of starting again and if the dyspnea increases an operation, either low forceps or Cesarean must be done in spite of the poor chances that it offers. An expectant policy at this time offers, I think, a poorer one.

If the woman is not in labor this treatment affords a very good chance of recovery. We have had only one death from pulmonary edema when the patient was not in labor and this was during her third attack. When the patient is not in labor we have used oxygen inhalations from a closed inhaler with great benefit to the cyanosis and decrease in the dyspnea and have also noted a slight slowing of the heart rate. The oxygen used was diluted with about one-third air and was given during alternate fifteen minute periods. There is no indication for operative interference in these cases unless the above measures do not bring about improvement, and as we have said they usually do so.

*Mild Cases.* When the patient shows only the lesser grades of failure during pregnancy she should be carefully guarded from exertions which cause shortness of breath or palpitation, for if such exertion is persisted in, the result will be cardiac overstrain and severe failure. A thorough course of digitalis lasting for a month

or six weeks will be found to improve the compensation of these less severe patients to some extent at least, and should be used in addition to the restriction of activity. We have had 3 instances in our series of acute severe failure with edema of the lungs coming on as a result of sexual intercourse after the fifth month, and 1 instance following a quarrel with the husband, so that these things must be warned against.

Long continued rest in bed is not necessary for these patients unless the result of allowing them to be up is the appearance of rapid pulse and dyspnea on such exertions as walking about the house. If the compensation is as poor as this, though, they are to be considered as in the serious class and the question of treatment should be approached as has already been outlined.

*Permanent Effect.* I am as yet unprepared to say whether or not pregnancy has a permanently bad effect upon the mothers' heart. We have been able to follow up so few cases and the time of observation is so short that I cannot yet feel sure of the answer. It is, I think, in view and seems to depend a great deal upon whether or not the pregnancy and labor were associated with severe heart failure, as well as upon the character of the postpartum treatment of the cardiac condition.

**Summary.** It should be evident from what I have said that it is not my feeling that abortion is often indicated for women with heart disease. Most of them will go through very well indeed, but it is our urgent duty to find some means of picking out those cases that will not go through without developing serious symptoms.

Cardiac failure is the thing which we fear in all cases, and we should be guided in our prognosis and treatment by the presence or absence of symptoms or signs of cardiac failure and by the degree of severity of these when present. The pathological condition is of much less importance than the physiologic reactions.

With proper observation and treatment severe cardiac failure should not occur during pregnancy, for if medical treatment does now ward it off, then interference is indicated. Even during labor its occurrence should be rare with careful observation and a promptly performed forceps or Cesarean section if severe failure seems imminent.

Operation should not be withheld at any stage, even though the signs of failure are slight, if they are seen to be growing progressively worse under proper medical treatment. It is better to operate when the failure is moderate than to have to do so when it is severe.

By such a coördination of medical and surgical treatment I feel sure that it will be possible to obtain more live babies and to have fewer maternal deaths than any of the figures which have so far been published. In our series the maternal mortality of the serious group was 26 per cent and of all cases 10 per cent. I feel that this is unnecessarily large and should be capable of reduction by more than half.

## THE MECHANISM OF ELIMINATION OF BACTERIA FROM THE RESPIRATORY TRACT.

BY ARTHUR L. BLOOMFIELD, M.D.,

BALTIMORE.

(From the Biological Division of the Medical Clinic, Johns Hopkins Hospital and Medical School.)

As long ago as 1868, Lister<sup>1</sup> noted that penetration of the lung by a fractured rib did not lead to infection of the pleural cavity even though the latter was brought in contact with the outer world by means of the inspired air. This observation was eventually followed by systematic studies which showed that in health the lungs are entirely or almost entirely bacteria-free, and a similar state of affairs was found to exist in the deeper nasal passages. The means whereby this condition of relative sterility is maintained has been carefully worked out, but the possibility of a similar protective mechanism in the mouth does not seem to have been entertained by those interested in the contiguous portions of the air passages. On the contrary, it has been generally assumed that the buccal cavity may be likened to an open Petri plate filled with a medium favorable for any entering bacteria, and superficial support for this idea comes from the actual identification of numerous varieties of organisms both saprophytic and pathogenic in cultures made from the mouth.

In the course of experiments made in the past three years we have been able to show that despite the presence of a profuse indigenous flora the mouth is as adequately protected against the colonization of foreign bacteria as are the lungs or deeper nasal passages. It is the present purpose, therefore, to review what information is at hand about the whole question of the protective mechanism of the upper air passages and to indicate its significance in relation to the spread of infectious disease. One may consider in the case of each of the various regions (mouth, nasal passages and lungs) the following factors of possible importance: (a) anatomic conditions; (b) the flushing mechanism; (c) bactericidal action of secretions; (d) reaction of secretions; (e) the antagonistic action toward invaders of the indigenous flora, and (f) phagocytosis.

**The Protective Mechanism of the Mouth.** As will be seen later, the presence of bacteria is avoided in the case of the nose and lungs largely by anatomic conditions which prevent the entry of organisms into these regions. It is of interest that the anatomic structure of the mouth does not in itself seem designed to prevent invasion. Inasmuch as the function of the mouth, as entrance to the alimentary canal, makes it impossible to avoid the con-

stant introduction of bacteria, a mechanism has been developed which acts by elimination rather than by filtration. But before discussing the details of this mechanism we may outline briefly the demand made upon it as well as what is actually accomplished by it. A host of foreign organisms is continually entering the buccal cavity. Of these the largest element is that carried in with food and drink. Milk, for example, usually contains many organisms, and various kinds of food, such as cheese, are swarming with bacteria and moulds. Fingers, cigarettes, stamps, and in the case of children, foreign objects of all sorts with bacterial content varying in kind and in extent, also make their way into the mouth, and finally a smaller number of organisms is constantly being inhaled. But if repeated throat cultures are made in normal people one finds not the diverse and variable flora which would be expected but a relatively simple and constant one. Revealed by aërobic methods there are a few predominating groups: The non-hemolytic streptococci, the Gram-negative cocci, diphtheroids and staphylococci—none of them organisms which are abundantly present in food or in the air. In addition one may find a miscellaneous group of transient bacteria which are present only for brief periods of time and are clearly intercepted by the culture swab in their passage through the mouth. Foreign pathogenic organisms are rarely found over long periods of time save when associated with a local focus of infection. In summary then there is evidently a rapid and effective elimination of the horde of incoming organisms whereby they are segregated from the normal indigenous flora.

An analysis of this process of elimination indicates that it is accomplished mainly by a system of flushing which operates in two ways: In the first place the gross act of swallowing propels the major portion of ingested material by forcible contractions of the muscular masses of tongue and pharynx directly into the esophagus. If a suspension of charcoal or a solution of a dye is swallowed there is intense staining of the dorsum of the tongue, of the palate and of the cheeks, but little or none of the sublingual space, tonsils or upper pharynx.<sup>2</sup> Furthermore, if a suspension of bacteria containing many million organisms per cubic centimeter is ingested and cultures are then made from various sites in the mouth and throat, relatively few colonies are recovered, and these are confined largely to the tongue.<sup>3</sup> In one such experiment nine colonies of the organism introduced grew in the culture from the pharynx and less than fifty were obtained from the tonsils. The swallowing mechanism operates therefore toward a rapid and direct removal of material without any churning action or tendency toward unnecessary contamination of the whole mouth cavity and without forcible implantation of many bacteria upon the mucous membranes.

In association with the above crude system of flushing a more highly organized mode of elimination may be demonstrated. If foreign particles or bacteria are implanted directly on the mucous membranes of the tongue, tonsil or pharynx it is found that they can no longer be readily dislodged. They adhere firmly in the tenacious mucus and are not removed by such procedures as rinsing or gargling. But once fastened in this way the particle or organism is drawn rapidly backward by a series of suction currents and is swallowed. The paths of these currents are quite direct. Bacteria implanted on the right side of the tongue, for example, travel backward on this side without crossing the midline and without contaminating the tonsil unless the latter is prominent; from the tonsil or pharynx they always move toward the esophagus—never forward into the mouth.<sup>2 3</sup>

The net effect of the operation of this mechanism we have tested by experimentally introducing various bacteria into the mouths of men. The general result has been that within twenty-four hours such organisms as the colon bacillus, staphylococcus, influenza bacillus, streptococcus and Friedländer bacillus are entirely eliminated.<sup>4</sup> It would appear, therefore, that the chance foreign pathogen introduced by natural means would ordinarily have but little chance of colonizing.\*

In this connection a word may be said about the function of the tonsils. As pointed out by various writers, for example, Crowe,<sup>5</sup> it is generally believed that the ring of lymphoid tissue in the pharynx acts as a barrier which protects the lower air passages by catching up bacteria which enter the mouth or nose. Many organisms undoubtedly do enter the tonsil crypts, but in view of the experiments reported above<sup>2</sup> it seems that such invasion occurs rather in spite of the mechanism which tends to spare the tonsils than as a beneficial event. Few would claim nowadays that the tonsils which have come to be regarded as notoriously injurious foci of infection serve any useful protective function.

While the flushing mechanism outlined above undoubtedly constitutes the major or first line of defence against colonization of bacteria in the buccal cavity, there are other factors to be considered. The bactericidal action of the saliva is certainly of some importance. While the literature on this subject is confusing and unsatisfactory,<sup>6</sup> as it deals only with test tube experiments which can hardly be applied to actual conditions in the mouth, it has been possible to show in the case of at least one variety of bacteria—*sarcina lutea*—that the saliva exerts a rapid actual destructive action *in vivo*: killing the organisms within fifteen minutes to one hour.<sup>7</sup> It may be that other organisms are similarly destroyed, but even in cases in which there is no true bactericidal

\* We use this term to indicate a biologic reaction between the organism and the host which allows the growth *in situ* of the former.

action there may be an inhibitory or bacteriostatic effect. This is a complex question of great interest which requires much more study. It seems of particular importance because even a slight bacteriostatic effect may be adequate to inhibit the activity of a foreign organism until it can be eliminated by the flushing mechanism.

The reaction of the mouth secretions must be considered apart from their other qualities. Recent work has brought out the tremendous importance of hydrogen-ion concentration in the growth of bacteria and of tissues *in vitro*,<sup>8</sup> and the question is raised whether reaction is not influential in favoring or inhibiting growth *in vivo* as well. It is suggestive that the reaction of most salivas— $p^H$  6.0— $p^H$  7.3—is more acid than that which has been found to be the optimum for growth of pathogenic bacteria such as pneumococci, streptococci, and influenza bacilli in the test tube—namely  $p^H$  7.4— $p^H$  7.6. In fact the  $p^H$  of the majority of human salivas is greater than that which allows initiation of pneumococcus growth at all in artificial media.<sup>10</sup> One may then safely conclude that the reaction of the mouth secretions does not favor most foreign bacteria; to what extent it actually has an inhibitory effect of practical importance cannot be definitely stated as yet.

Still another possible factor is that of antagonistic action against foreign bacteria by the normal mouth flora. Test-tube experiments seem of little value in settling this point and experimental approach is difficult, but occasional observations indicate that one organism may dislodge another. Patient F. yielded hemolytic influenza bacilli in large numbers on three successive cultures from the pharynx. Two days after the last examination he developed an acute tonsillitis. Thereafter on numerous cultures made over a period of two months hemolytic streptococci were present in almost pure culture, but hemolytic influenza bacilli were no longer found. Patient A. on first culture showed mixed throat flora. On the second and third cultures the plates were covered with Friedländer bacilli. There had been no clinical reaction. Two more cultures were made, using a system of dilutions so that only twenty-five to fifty colonies of Friedländer bacilli were present on each plate. Even with this dilution, which probably eliminated overgrowth on the plates, no other organisms were present, indicating that they were largely or entirely absent at the site of culture. It may be therefore that a balance of power among the various inhabitants of the mouth is an accessory factor in inhibiting the growth and colonization of foreign invaders.

Although the present discussion concerns itself with the means whereby colonization or establishment of growth on respiratory mucous membranes is prevented, for the sake of completeness one must mention the last line of defence, namely, the protective activi-



ties of the body fluids and cells. This point is brought up because there is evidence that even without production of disease occasional penetration of intact mucous membranes by bacteria may occur.<sup>11</sup> Whether in such cases at least a physiologic lack of continuity exists is a much-disputed academic question, which need not be discussed in the present connection. The point of importance is that even should a foreign organism escape elimination of the flushing mechanism—caught up, let us say, in a crevice of the mucous membrane—there still remain possible modes of effective disposal.

**The Nasal Passages.** While the protective mechanism of the mouth consists mainly of elimination, that of the nose operates especially by prevention of invasion; anatomic considerations are unimportant in the former, essential in the latter. Entry of bacteria into the nose follows almost always the inhalation of bacteria-laden dust or droplets; direct introduction, which is the usual event in the case of the mouth, rarely occurs. If one considers the structure of the nasal passages it is apparent that no direct open path exists in the line of the air currents but that such currents immediately impinge upon the turbinated bones. Furthermore, these are so constructed that the stream of air is not only broken up but is deflected in numerous directions. A satisfactory demonstration of this fact is obtained by study of frontal sections through the nasal passages at various levels. As a matter of fact, most of the inhaled bacteria are arrested (probably by the network of moist vibrissæ) very near the anterior nares, as shown by Hasslauer,<sup>12</sup> Thompson and Hewlett<sup>13</sup> and others, who found large numbers of organisms at the nasal orifices and few or none in the deeper air passages. But inasmuch as the nasal mucosa is covered with a film of mucus, any organisms which do penetrate are promptly caught up and rapidly swept by the current of the ciliated epithelium toward the pharynx and esophagus. Thompson and Hewlett noted the speed of the ciliary current in the frog's pharynx to be as great as one inch per minute, and by actual experiment we have found that organisms placed in the nose may be recovered from the pharynx after as short a space of time as ten minutes. In summary, then, we have an effective self-cleaning filter which purifies the air of bacteria before it enters the lungs.

Whether or not other elements enter into the protective mechanism of the nasal passages is uncertain. Thompson and Hewlett obtained evidence that *bacillus prodigiosus* was destroyed in the nose, and conclude without justification that few or no bacteria introduced into the nares can reach the pharynx alive. There are also certain incomplete and dubious experiments on record as to the bactericidal action of the nasal secretions<sup>14</sup> *in vitro*. This part of the subject requires much further study before final statements can be made.

**The Lungs.** The question of how the lungs are guarded against infection is one of great interest, and in considering this matter our main point of approach must be the outstanding fact that in health few or no bacteria are present below the larynx. While direct evidence from human beings is not readily obtainable, cultures made from the lungs of healthy animals are almost uniformly sterile. The most significant observations on this point with which we are familiar are those of Heuer.<sup>15</sup> This observer, in the course of experimental excision of the lung in dogs, made numerous cultures from the bronchial stump. In no case were any organisms found. On the other hand it is known from post-mortem appearances that dust and carbon and metal particles do reach the lung, and it seems very likely that some few bacteria are introduced as well. The history of this question is an interesting one and many observations are on record which seem contradictory. Paul,<sup>16</sup> Neuninger<sup>17</sup> and Quesnil<sup>18</sup> give a comprehensive review of the literature on the subject of the bacterial content of the normal lung and attempt to reconcile the diverse findings of various writers. When one considers that some studies were made a considerable length of time after death, some in cases in which there had been a long agonal period, and that in others the subjects were animals who burrow in fodder and inhale heavily bacteria-laden dust, it is clear that one can draw no final conclusion as to the usual state of affairs in man. It seems certain, however, that in health and under average conditions of dust exposure it is only the occasional organism which penetrates below the larynx. It appears then that the protective mechanism of the lung includes two main factors: (a) An anatomic structure which cuts off most of the organisms from the inspired air, and (b) a process which destroys or eliminates the few which do penetrate.

The anatomic element seems of greatest importance. As pointed out above the entering current of air, whether through nose or mouth, is deflected against complex mucous-covered surfaces which catch up bacteria and act as filters. In regard to the question of how many bacteria actually do pass these barriers the experiments of Paul<sup>16</sup> are of special significance. This observer placed rabbits in a glass chamber into which a suspension of bacillus prodigiosus was sprayed. After one-half hour of this treatment the animals were killed and cultures were made from the lungs under proper precautions. Prodigiosus was invariably found, sometimes as many as 500,000 colonies in part of one lung. By an ingenious calculation, Paul reached the conclusion that 4 per cent of the inspired organisms had reached the lung, and reasoned further that under spontaneous conditions a similar fraction of the inspired bacteria might penetrate. We are not convinced that this reasoning is correct—probably there is a proportionate decrease in the number of bacteria reaching the lung as the number

## BLOOMFIELD: ELIMINATION OF BACTERIA

in the air decreases, but none the less the fact remains that the filter is not a perfect one and that at times organisms do actually penetrate beyond the larynx. Paul also showed by a rather artificial experiment in which he introduced a foamy suspension of prodigious into the mouths of rabbits that droplets formed by the bursting of bubbles *in situ* might be inhaled, as indicated by subsequent recovery of the organisms from the lung. In actual life the bacterial content of the air is variable. In dusty rooms it may be as great as several hundred thousand per cubic meter, but this is unusual. The chances, therefore, of pathogenic bacteria reaching the lungs of normal people by direct inhalation are slight.

The main factor then in the protective mechanism of the lung is a highly effective but not infallible filter. What is the fate of the few organisms which do pass the larynx in health? Three possibilities must be considered. The bacteria may be removed, they may be destroyed in the lung or they may set up disease. The trachea and larger bronchi are lined with ciliated epithelium which sweeps toward the larynx. We know that inhaled dust is carried up by this process and expectorated mixed with mucus; doubtless bacteria are eliminated in the same way. That this is not the only element involved in removing bacteria from the lung is indicated by an experiment such as the following: Paul sprayed rabbits with prodigious and found that after twenty-four hours only 1/35000 as many colonies were present in the lung as after the treatment, whereas in a similar experiment with *subtilis* spores 6/11 of the number originally inhaled could be recovered after twenty-four hours. This would suggest some other process besides a simple mechanical removal. Simultaneous cultures from lungs and bronchial nodes<sup>18</sup> indicate that many bacteria are removed by lymphatic drainage, and finally some organisms finding themselves in unfavorable surroundings may die *in situ* in the lung.

In summary, then, in health a very effective protective mechanism exists which operates against the colonization of bacteria in the lung. The main element is a filtration system which allows only few organisms to enter. These, unless they produce disease, are eliminated by the ciliary current, by dying *in situ* or by being carried off through the lymphatics.

Above we have sketched briefly the *modus operandi* of the protective mechanism against the colonization of bacteria in the respiratory tract, recognizing that our knowledge is still in the most rudimentary stage. The essential point, however, seems to be a system of mechanical filtration and flushing aided by influences which temporarily arrest the aggressiveness\* of foreign

\* This term is not used here in the technical sense.

organisms (reaction and bacteriostatic effect of saliva, antagonistic action of mouth bacteria) until they can be removed.

So far we have stated the case altogether in favor of the host and against the invader. But experience shows that the protective mechanism, while theoretically adequate, often breaks down in actual fact with consequent colonization of foreign bacteria and production of disease. It seems pertinent, therefore, to examine the matter from the other side and to analyze the factors which lead to failure of the protective mechanism.

1. *Dosage.* There exist certain bacteria of such virulence that a single cell may suffice to infect a susceptible animal. On the other hand we find organisms of such a nature that no number however great seems capable of setting up disease. In the vast majority of cases, however, it is dosage which is the determining factor in experimental infection. Numerous observations indicate its importance in human disease also. We may perhaps think of infection in terms of a balance struck between the race and various types of bacterial invaders which tends to keep up an average incidence of infectious diseases among large groups of people. But in the individual case an overwhelming dose of organisms may regularly produce disease. It seems altogether reasonable to suppose that the protective mechanism of the respiratory passages, unless it were perfect, in its action would be more effective against a smaller than against a larger dose of foreign pathogens. While single organisms successively introduced might be disposed of thousands of times before a weak point in the defence could be taken advantage of, some one or another of a thousand organisms simultaneously introduced might find favorable conditions for colonization or invasion even though all the rest of the group were eliminated. It is likely therefore that, other things being equal, dosage is of importance in explaining certain instances of breakdown of the protective mechanism.

2. *Anatomical Features.* In the experiments which were made on the fate of charcoal particles introduced into the mouth it was noted that anatomical variations frequently led to a disturbance of the normal currents of removal. In one instance it was possible to watch for several hours a small mass of carbon particles which had been arrested above a bit of protruding lymphoid tissue on the posterior pharyngeal wall. Furthermore, particles and bacteria must be frequently caught up in the tonsillar crevices despite their relatively protected position. It may well be then that an organism which would be harmless if promptly eliminated may be enabled to unfold pathologic activity if arrested in the throat for any length of time.

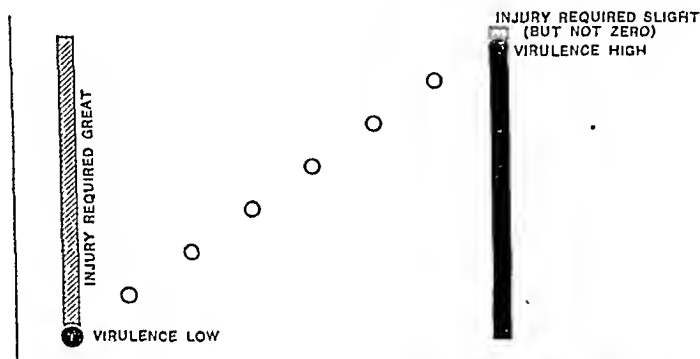
3. *Lag.* An old observation in bacteriology is to the effect that a single organism inoculated into a flask of broth may fail to grow, whereas a larger inoculation may result in profuse develop-

ment. Further study of this phenomenon has shown that the various members of a culture are not equally viable at all ages and that senescence sets in early. If such senescent organisms are transferred to a fresh medium a latent period exists before active growth is again resumed by the culture as a whole. This phenomenon of lag has been carefully studied by Chesney,<sup>19</sup> who has worked out its laws especially in the case of pneumococcus. But pathogenic organisms as they enter the body from certain outside sources are probably not always in an active vegetative state. When dried in dust or on objects they usually assume an inactive or resting form. It is fair to conclude, therefore, that many pathogenic organisms as they enter the respiratory passages are in a state of greater or less inhibition. Such inhibition may be important in allowing their removal before activity is resumed. Conversely, if the organism enters the mouth while in an actively vegetative state its chances of colonization should be greater. Such a condition of affairs would apply especially to organisms transferred directly by cough through the air from one individual to another. It is of interest that in epidemics of acute infections such as those which occurred in the army camps one was dealing with a concentration of individuals and hence with a rapid transmission of organisms by very direct routes, indicating that a highly vegetative state of the bacteria existed.

4. *Injuries.* Perhaps the most important factor leading to a breakdown of the protective mechanism is some type of injury. Before taking up this point, however, a few words must be said about virulence and resistance.

*Virulence.* As a rule this term has been loosely used to indicate that the organism in question is producing a more or less severe and highly contagious form of disease. More exact definition is however necessary; in other words, does a highly virulent organism possess intrinsically any greater invasive power than a less virulent member of the same species, and if the two were deposited on a perfectly intact and healthy mucous membrane would the one be able to invade and produce disease while the other could not? It seems that definite evidence of any such difference is lacking, but that in the case of the virulent organism a much slighter injury or defect and perhaps an injury or defect of a different sort is adequate to allow invasion. In the case of an extremely virulent organism one can picture the requisite injury being so slight as to approach zero. The point may best be brought out by a specific example such as streptococcus infection. Under ordinary conditions the streptococcus is clearly a secondary invader. Its role in terminal infections, in scarlet fever, in measles and in influenza may be mentioned. Here it unfolds its activities on tissue damaged by an independent primary process. During the war, following the rapid and extensive passage of strep-

tococci through large numbers of patients with measles, strains appeared which finally on superficial scrutiny seemed able to produce primary disease. It seems much more likely, however, that these exalted strains were simply able to take advantage of a minute lesion, perhaps a minute mechanical injury of the mucous membranes, which under ordinary circumstances would not suffice to allow the entry of an organism of average virulence. This idea is supported by the clinical observations of every type of transition between the streptococcus as an obvious secondary invader, and the streptococcus as an apparent primary invader. The situation may be diagrammed as follows:



In further support of this idea the following facts may be mentioned: (a) The usual prompt elimination of foreign organisms naturally or experimentally introduced into the upper air passages; (b) the corroborative evidence of the rarity of the production of certain diseases by direct contact such as lobar pneumonia; and (c) the fact that the incidence of a disease due to a highly "virulent" organism may be lower than that of a disease due to a less "virulent" one. For example, the incidence among pneumonia cases of type III infection is only about 10 per cent with a mortality rate of 50 per cent, whereas type I infections, which make up 25 to 30 per cent, of the whole, have a mortality of only 20 to 35 per cent.<sup>20</sup> Furthermore, the type III organism is more widely distributed among the population in general than type I. Clearly the invasive power of these organisms does not run parallel with the severity of the infection produced by them.

In summary, then, while the virulence of an organism may establish the mortality rate among those infected, and may to some extent determine the incidence of infection in so far as the highly virulent organism may take advantage of a slight injury to the host so that it can invade, in the last analysis the production of disease seems to be made possible by an injury or defect which is more or less independent of the organism. This generalization seems to apply to the common respiratory pathogens such as pneumococcus, streptococcus, meningococcus, and the influenza

bacillus. Whether other viruses such as the hypothetical ones of the acute exanthemata can produce their own injury requisite for invasion is still uncertain.

**Types of Injury Important in the Production of Respiratory Infection.**

Such injuries may be mechanical, thermal, chemical or infectious.

A. *Mechanical Injuries.* Purely mechanical injuries probably play only a minor part in facilitating infection. The mucous membranes, however, undoubtedly suffer constant slight traumata which may create portals of entry for highly virulent organisms. Such lesions may well account for many sepses of so-called cryptogenetic origin. They also undoubtedly play a part in the production of erysipelas. We have observed three cases of septicemia directly following the mechanical cleansing of tonsil crypts during the course of acute tonsillitis. Blake<sup>21</sup> was unable to produce pneumonia in monkeys by placing virulent cultures of pneumococci in the throat, but after injuring the trachea with a needle puncture invasion became possible. It is well established that postoperative lung abscess is due to the forcible inhalation of bacteria-laden bits of blood clot, following the elimination of the protective reflexes by the anesthetic. Disturbances of the cilia-bearing epithelium of the nose by operative measures often leads to subsequent chronic inflammation with colonization of bacteria. Finally, as an instance of mechanical disturbance of the bacteria eliminative mechanism, an observation made by us in a patient with bulbar palsy may be recorded. In this case *sarcina lutea* placed on the tongue was not removed by the usual suction currents but remained confined to the site of inoculation during the whole period of the experiment.

B. *Thermal Injuries.* The question of the relation of cold to respiratory infection is of interest. The recent thorough experiments of Mudd<sup>22</sup> and his associates indicate that thermal variations lead to marked vasomotor and secretory changes in the upper air passages. These writers bring a certain amount of evidence<sup>23</sup> that the bacterial flora may be modified following such reactions and give an important lead for further study.

C. *Chemical Injuries.* Chemical injuries may undoubtedly produce lesions which disturb the normal eliminative mechanism and allow bacterial invasion. Two prominent examples may be quoted: War-gas poisoning,<sup>24</sup> if of any degree of severity, is followed by bronchopneumonias and histologic studies of the tissues show the bacteria actually invading the mucous surfaces denuded of their protecting epithelium. Poisoning with certain arsenicals allied to arsphenamine is accompanied by a severe erythema of the respiratory mucosa. This is soon followed by a bronchopneumonia clearly secondary to the chemical injury. We have observed three instances of this condition.

D. *Infection.* In this group falls perhaps the most important kind of injury which leads to secondary bacterial invasion in the upper respiratory tract. The role of measles, scarlet fever, influenza,

smallpox and the exanthemata in general in allowing secondary infection is notable. In these diseases the "erythema" of the respiratory mucosa is associated with a disturbance of the normal protective mechanism following which secondary infections with various organisms readily occur. Olitzky and Gates<sup>25</sup> bring experimental support for this idea in the case of influenza. The common cold frequently draws in its wake a series of obvious minor secondary infections, and perhaps just as often serves as the predisposing factor for more serious infections. A careful clinical study of such diseases as lobar pneumonia and meningitis might disclose such preliminary injuries.

5. *Adaptation.* However much one may try to reduce the protective mechanism to a concrete basis there still remains a factor to be considered, namely, inherent adaptation of certain bacteria to growth on human mucous membranes. In another place we have presented evidence that some bacteria not members of the normal flora which are potentially capable of producing disease may become more or less completely adapted to free growth on normal mucous membranes.<sup>26</sup> This is true of influenza bacilli, green-producing streptococci and probably many other bacteria. Under such conditions the organism is not eliminated but is at hand over long periods of time. Then if proper accessory conditions arise invasion and disease may follow.

*Discussion.* The problem of infection may be approached from either of two standpoints—that of infection in groups of people or that of infection in the individual. Under the former head there are to be considered the broad general questions of the spread and incidence of disease—the nature and course of epidemics, the seasonal occurrence of various diseases, and their geographical distribution. A great stock of information in regard to these matters has been accumulated through the recording of gross facts and to a lesser extent by experimental studies of epidemics in animals, but the final determination of the laws governing infection has not yet been achieved. Contradictions constantly come up. In the case of a pandemic of influenza, for example, it seems established from the general sequence of events that we are dealing with a disease due to a living virus and one which is highly contagious. But when one attempts to explain the details of its spread, insurmountable difficulties immediately arise. The high incidence of the disease in certain localities among special groups of people with the sparing of others, the sparing of particular individuals for a considerable length of time (despite constant exposure) with ultimate infection, and the question of the sporadic case may be mentioned as examples of the difficulties which present themselves. Again, in the case of lobar pneumonia, despite the evidence in favor of transmission by carriers or dust, these general principles seem inadequate in working out the origin of individual infections.

Aside from such broad considerations we have to deal with



the problem of infection in the individual, and here a different approach must be used. The general facts of epidemiology tell the number of people in a community likely to be affected by a certain disease under given conditions, a solution of the problem of infection in the individual will tell why A. is affected rather than B. and C. rather than D.

In an attempt to clarify this latter phase of infection with reference to respiratory disease the above analysis is presented. It has seemed profitable to avoid, as far as possible, such vague terms as virulence and resistance and to reduce the facts to concrete terms. The most general conclusion is to the effect that there exists in the respiratory passages—nose, throat, mouth and lungs—a mechanism which tends to eliminate foreign particles and bacteria.

It is also clear that this eliminative mechanism has many imperfections and that in actual practice it often breaks down; it should be thought of rather as a tendency than as a rigidly efficient process, as relative and not as absolute, differing with different organisms and with a host of secondary conditions.

Again, it seems unwise to go too far in assigning purposeful protective qualities to the eliminative mechanism, and we wish merely to stress and to classify facts which may be helpful in explaining the means whereby colonization of bacteria is prevented or favored. A word of speculation may however be allowable. The classical viewpoint in regard to recovery from infection, or protection against infection, based on theories of humoral immunity, assumes a positively destructive action in disposing of foreign bacteria. It is now becoming more and more evident that the simple absence of favorable circumstances for the organism may be just as effective as any positively destructive action. Test-tube experiments are very clear on this point. Pneumococci, for example, when growth is once started may multiply in broth until a limiting reaction of  $p^H$  5 is reached. Growth cannot, however, be initiated below  $p^H$  7 in the same medium. In studying the action of dyes on bacteria it has also been shown that inhibitory or bacteriostatic effects are perhaps of as much importance as actual bactericidal action. It seems that this principle should be extended to human infection and that the respiratory protective mechanism is perhaps largely a matter of absence of favorable conditions for the foreign organism rather than any positively destructive process, although such action may be shown in certain instances. The main point, then, which we wish to make is the following. It has usually been assumed that the presumption was in favor of the invading organism and that the body was obliged to call forth special protective process to prevent infection. Now it is clear that the microorganism is, on the whole, at a disadvantage and that no special response is, as a rule, required to dispose of it, but that special favoring circumstances for the organism must be present before infection can take place.

# REFERENCES.

1. British Med. Jour., July 18, 1868 (quoted by Thompson and Hewlett).
2. Bloomfield, A. L.: The Circulation of Foreign Particles in the Mouth, *Am. Rev. Tuberc.*, 1922, 5, 903.
3. Bloomfield, A. L.: The Circulation of Bacteria in the Mouth, *Bull. Johns Hopkins Hosp.*, 1922, 33, 145.
4. Bloomfield, A. L.: The Upper Air Passages as an Environment for Bacterial Growth, *Am. Rev. Tuberc.*, 1920, 4, 247.
5. Crowe, S. J.: The Relation of Tonsillar and Nasopharyngeal Infections to General Systemic Disorders, *Bull. Johns Hopkins Hosp.*, 1917, 28, 1.
6. See Sanarelli: *Centralbl. f. Bacteriol.*, 1891, 1 Abt., Bd. 10, 25. Barnes, B. S.: *Tr. Chicago Path. Soc.*, 1907-09, 8, 249.
7. Bloomfield, A. L.: The Fate of Bacteria Introduced into the Upper Air Passages, *Bull. Johns Hopkins Hosp.*, 1919, 30, 347.
8. See Avery, O. T.: *Jour. Exper. Med.*, 1919, 29, 215. Fischer, Albert: *Jour. Exper. Med.*, 1921, 24, 447.
9. Bloomfield, A. L.: The Reaction of the Saliva, *Bull. Johns Hopkins Hosp.*, 1921, 31, 118.
10. Avery, O. T.: *Jour. Exper. Med.*, 1919, 30, 359.
11. See Zinsser, Hans: *Infection and Resistance*, 2d ed., p. 13.
12. Hasslauer: *Centralbl. f. Bakteriologie*, 1906, 1 Abt. Ref., Bd. 37, 1.
13. Thompson and Hewlett: *Lancet*, 1896, 1, 86.
14. See Wurtz and Lermoyez: *Am. des mal. de l'oreille*, 1893. And Calvino, V. E. M.: *Arch. Ital. di Otolog.*, etc., 1891, Bd. 10, 25.
15. Heuer, G. J.: Personal communication.
16. Paul, Ludwig: *Ztschr. f. Hyg.*, 1902, 40, 468.
17. Neuninger, O.: *Ztschr. f. Hyg.*, 1901, 38, 94.
18. Quesnil, U.: *Ztschr. f. Hyg.*, 1902, 40, 505.
19. Chesney, A. M.: *Jour. Exper. Med.*, 1916, 24, 387.
20. Avery, Chiekring, Cole and Doehez: *Monographs of the Rockefeller Institute for Medical Research*, No. 7. Acute Lobar Pneumonia.
21. Blake, F. G. and Cecil, R. L.: *Jour. Exper. Med.*, 1920, 31, 403.
22. Mudd, Goldman and Grant: *Jour. Infect. Dis.*, 1921, 34, 11.
23. Mudd, Grant and Goldmann: *Jour. Infect. Dis.*, 1921, 29, 151.
24. Winternitz, M. C.: *Jour. Exper. Med.*, 1919, 29, 537.
25. Olitzky, P. and Gates, F.: *Jour. Exper. Med.*, 1921, 34, 1.
26. Bloomfield, A. L.: The Significance of Hemolytic Influenza Bacilli, *Bull. Johns Hopkins Hosp.*, 1921, 22, 378.

## TWO HUNDRED SYPHILITIC PATIENTS WHOSE CHIEF COMPLAINT WAS "STOMACH TROUBLE," AN INTERPRETATIVE ANALYSIS OF THE DIAGNOSIS OF SYPHILIS IN CONSULTANT MEDICAL PRACTICE.

By JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, MAYO FOUNDATION GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA,

AND

PHILIP W. BROWN, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

(From the Section on Dermatology and Syphilology, Mayo Clinic.)

CABOT, in the second edition of *Differential Diagnosis*, directed the attention of the profession to dyspepsia as a medical complaint.

In his experience cardiac disease stood at the head of the list of pathologic conditions which were expressed in the consulting room in this particular manner. Cabot gives due emphasis to the importance of an examination of the spinal fluid and of a neurologic examination of patients who may have syphilis underlying their gastric complaints without gross evidence of tabes. Contributions to the meaning of "stomach trouble" in syphilis have been made from the Mayo Clinic, particularly by Eusterman and Carman, who have dealt with various aspects of the clinical, roentgenologic, and pathologic picture of syphilitic gastric disease. It occurred to us, however, that an analysis from the standpoint of the patient rather than of the finished diagnosis might yield results of value in the general diagnostic problem of syphilis, which is our primary concern. Few items in the story of a medical case in general are of more import than the presenting symptom, and yet in certain aspects of syphilis especially, few items tell so little of the true state of affairs.

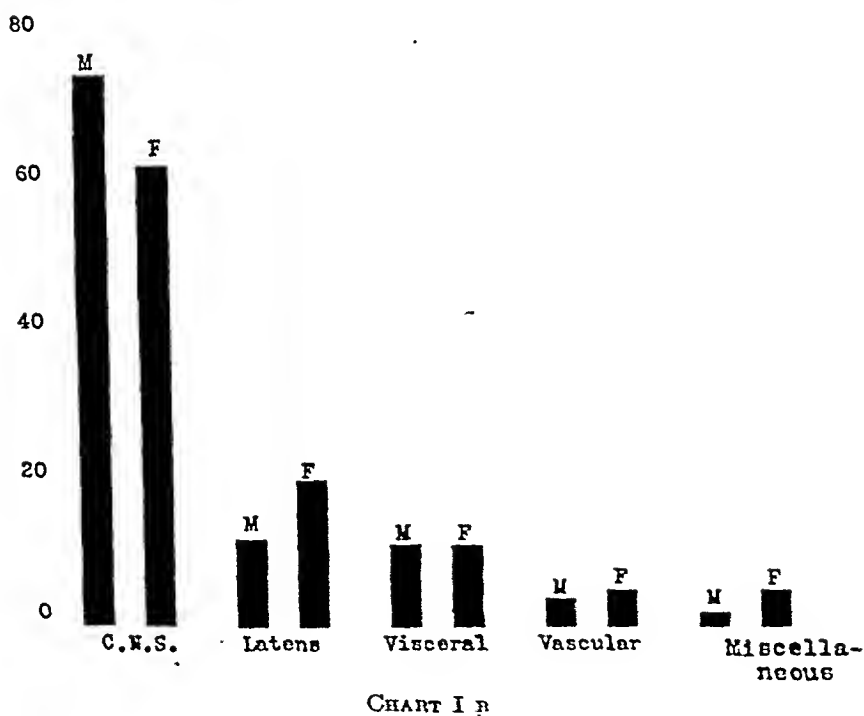
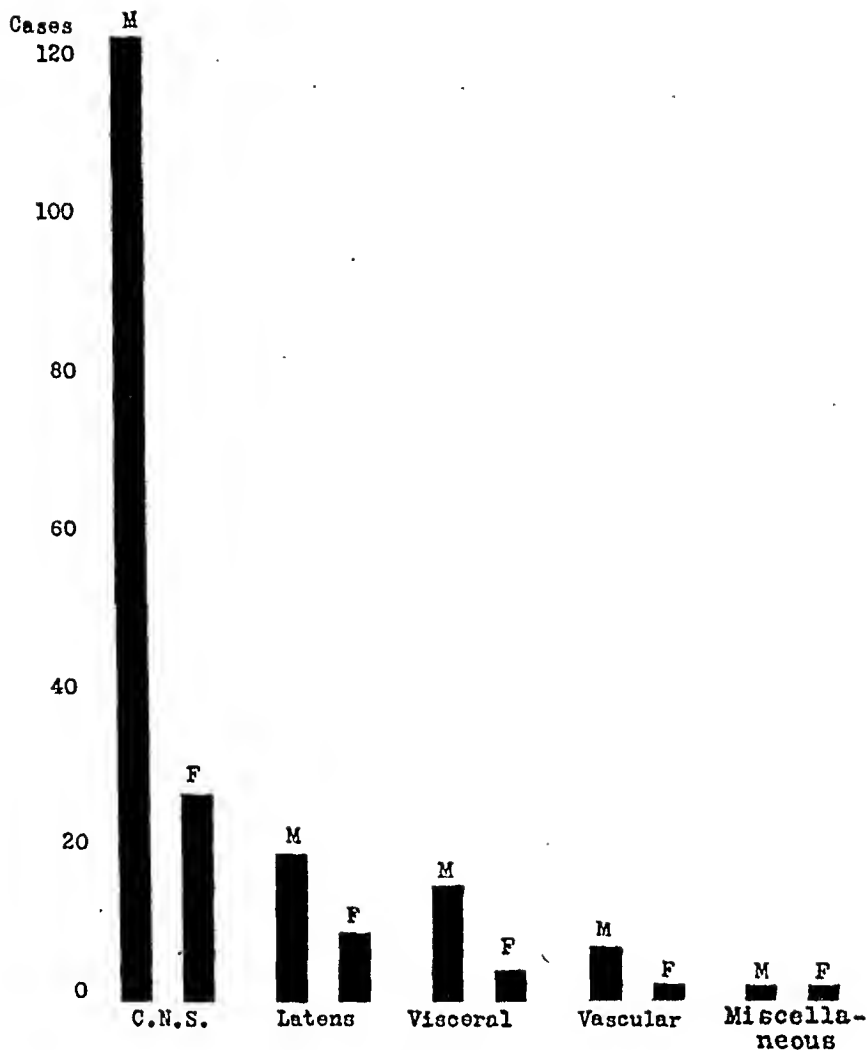
In order not to produce an artificial picture of the meaning of gastric complaint<sup>1</sup> in relation to syphilis seen in a diagnostic clinic, we adopted the following methods of approach. All patients considered in our survey had been shown undoubtedly to have syphilis. The search was confined to records of the Section on Dermatology and Syphilology for the years 1920-1921 during which time we have approximated our highest efficiency in the detection of the disease. More than two-thirds of the cases are from the files of 1920. All patients who presented a gastric complaint were included in the series, without any other form of selection being exercised. Of 200 patients thus included, 87 per cent were found to have rated stomach trouble as their chief complaint.

On analysis of this group of 200 cases, it appears that the majority of syphilitic patients who have gastric complaints have neurosyphilis (70 per cent). In the entire series of 200 patients, only 20 presented organic lesions of the stomach or the duodenum and only 9 presented lesions of the heart.

Many interesting sidelights on the general diagnostic problem which syphilis, especially late syphilis, presents in modern medicine developed from this study. These may be summarized as follows:

The age of the large proportion of the patients was between thirty-five and forty-five years, which previous surveys have shown to be a little earlier than the average age incidence of late syphilitic complications in general. It is in line with the experience of others who have studied syphilis statistically that a much larger proportion of men than women have neurosyphilis. Our first impressions were similar. Chart 1A suggests this preponderance of men over women. But if a chart is constructed to represent the number of each sex with

<sup>1</sup> By gastric complaint we mean that the patient included in his voluntary account of his symptoms, such items as vomiting, nausea, pain in the stomach, indigestion, burning and belching and stomach trouble.



a special type of manifestation in comparison with the number of the same sex presenting themselves with syphilis (Chart 1B), the difference between the sexes is seen to be more apparent than real. We believe that this form of statistical error is more common than is generally realized.

The history of syphilis is the conventional first approach to a diagnosis of the disease in ordinary practice. If the patient denies infection, investigation often goes no further. The fallibilities of this approach cannot be too often emphasized. As compared with men, women give a history of syphilis in the later years of the disease in a proportion of only 1 to 2.5, or somewhat more than one-third as often. The proportion of men who had no recognizable secondary lesions was 60 per cent, of women 70 per cent. Inability to obtain a history of secondaries, then, is evidently of small value in eliminating syphilis. In a general way all late syphilis may be traced to failure to recognize or adequately to treat the primary phase of the disease. The chancre was apparently correctly diagnosed in only 62 per cent of 109 male patients who gave a history of a suspicious primary lesion. The number of female patients who gave a history of chancre was too small for satisfactory comparison. This percentage of correct diagnosis of the primary lesion closely approximates an estimate of 70 per cent, recently obtained by us in patients with early primary and secondary syphilis who had been under observation by physicians before they came to the Clinic. It suggests that a diagnosis is made in only two-thirds of patients with syphilis who consult physicians early in the disease, and that even with modern diagnostic aids the average has not strikingly improved. Of the 60 per cent of our patients who gave suspicious histories, only 36 per cent had had diagnoses of syphilis before coming to the Clinic.

How was syphilis identified in this group of 200 patients who entered a medical and surgical clinic for the relief of stomach trouble? The patients were divided into two groups, those whose diagnosis had been made before entry, and those in whom it had been made afterward. The necessary data on diagnoses elsewhere were obtained from only 134 (Table I). The percentage of positives in the 200 cases is much higher on some items because of the inclusion of cases excluded from the diagnosis made elsewhere.

It was a matter of surprise to us that gastric syphilis, detectable by clinical and roentgenologic criteria, played so small a part in the final evaluation of a complaint of stomach trouble in clinical syphilis.

It is evident that the history of infection and the positive blood Wassermann reaction rank high in making a diagnosis of syphilis in general medical practice. The examination of the spinal fluid on the other hand, evidently of so much importance in our own identification of syphilis, plays little part in diagnosis elsewhere. Only

10 per cent of patients in the entire series had had an examination of the spinal fluid before entering the Clinic. About 50 per cent of the patients identified as syphilitic by neurologic signs only, had gastric crises with negative spinal fluid and negative blood Wassermann reactions.

TABLE I.—BASIS FOR DIAGNOSIS OF SYPHILIS IN 134 CASES OF GASTRIC COMPLAINTS.

	Diagnosed elsewhere 60 cases, per cent.	Not diagnosed elsewhere 74 cases, per cent.	All cases (200) after examina- tion in Clinic, per cent.
History of infection . . . . .	90	31	60.0
Positive blood Wassermann . . . . .	65	56	44.0
Positive spinal fluid . . . . .	6	44	59.0
Negative blood Wassermann and posi- tive spinal fluid . . . . .	5	28	41.0
Neurologic signs only . . . . .	7	9	16.0
Gastric syphilis . . . . .	1.5	3	4.0
Osseous syphilis . . . . .	3	0	1.5
Vascular syphilis . . . . .	3	0	4.5
Miscellaneous . . . . .	1	5	3.0
Probably non-syphilitic (duodenal and gastric ulcers) . . . . .	6	8	6.0

In a surprisingly small proportion stomach trouble was owing to something more or less obviously non-syphilitic, such as a duodenal or gastric ulcers. The very striking proportion of improvements obtained under treatment further supports the belief that demonstrable organic non-syphilitic lesions play only a small part in stomach trouble among syphilitic patients.

**Analysis of the Blood Wassermann Findings.** It is very evident that in the practice of the Mayo Clinic it is useless to expect late syphilis to yield in the aggregate more than 50 per cent of positive blood Wassermann reactions to aid in the diagnosis of the disease. This percentage has been repeatedly approximated in various surveys which we have undertaken. It has been a matter of some concern to learn the reason for this relatively low proportion of positives in order to decide whether or not the extensive use which we make of the examination of the spinal fluid is justified. An analysis of the results of Wassermann reactions in our series showed quite definitely that the 56 per cent of patients on whom we were unable to obtain positive blood Wassermann reactions in routine examinations were either intrinsically negative, or patients who had been subjected to treatment as soon as their positive reactions were discovered elsewhere, and later came to us with blood negative to the Wassermann test. A considerable proportion of patients who were negative to the Wassermann test on the blood, had positive spinal fluids. That this proportion of positive spinal fluids is materially higher than that of positive bloods is, we believe, evidence of the fundamental importance of the examina-

tion of the spinal fluid in the clinical study of late syphilis, and of its applicability to a variety of the problems of internal medicine in which a concealed and blood-Wassermann-negative syphilis may be a factor. Our experience suggests that when there is a reasonable suspicion of syphilis, such as is afforded by a history of a genital lesion, or when there are suspicious neurologic findings, the examination of the spinal fluid may be much more important than the gastric analysis and the roentgenogram which too often constitute the extent of the study. Certainly if the clinicians who examined our patients with stomach trouble, had been hidebound to a test meal and symptomatic study of these cases, or had been relieved of their suspicions with regard to syphilis by negative Wassermann reactions, many of the patients included in this series would have left the Clinic with their fundamental ailment unrecognized (Table II).

TABLE II.—81 PATIENTS WHO HAD HAD WASSERMANN TESTS ELSEWHERE.

Wassermann reaction on blood.	Treated outside the Clinic.	Not treated outside the Clinic.
Positive elsewhere; positive in Clinic . . . . .	5	7
Negative elsewhere; positive in Clinic . . . . .	2	10
Positive elsewhere; negative in Clinic . . . . .	27	3
Negative elsewhere; negative in Clinic . . . . .	22	5

112 PATIENTS WITH "STOMACH TROUBLE" AND NEGATIVE WASSERMANN REACTIONS ON THE BLOOD.

	Recently treated.	Not recently treated.	Total.
Negative Wassermann reaction on the blood; no examination of spinal fluid . . . . .	7	1	8
Negative Wassermann reaction on the blood; positive spinal fluid . . . . .	30	42	72 (69.2 per cent)
Negative Wassermann reaction on the blood; negative spinal fluid . . . . .	16	16	32 (30.7 per cent)

It is evident that the large proportion of our negative-blood-Wassermann reactions are obtained on treated patients, and that positive reactions are not infrequently obtained in patients who have been negative elsewhere. If then we are to make a sound objective diagnosis of syphilis, we must resort to the spinal fluid examination, which will yield 64 per cent positives when the blood, for one reason or another, is negative and fails to confirm our suspicion. The detailed analysis of the treatment status of the blood-Wassermann-negative patients is contained in Table II. Fifty-nine patients who had not been treated recently, nevertheless, had negative Wassermann reactions on the blood. These, therefore, are the true or intrinsic negatives. Of these intrinsically negative patients 42 (70 per cent) had positive spinal fluids. It is evident, therefore, that

from this angle also the spinal fluid examination assumes an exceedingly important place in the making of the diagnosis.

Estimating on the basis of 59 true negatives, we find that our Wassermann procedure, when not affected by treatment, should yield approximately 60 per cent positives, instead of the 44 per cent which we actually obtain under the conditions in which we are practising. With the very high proportion of tabetic neurosyphilis, and especially of gastric crises in the series, this is a reasonable proportion of positive results. Gennerich's estimate, one of the most recent for tabetic neurosyphilis, is 60 to 70 per cent positives on the blood in the first decade of the disease.

It is evident, therefore, that the conditions of consultant practice as we meet them cannot be satisfied by the use of the blood Wassermann reaction alone, which is already yielding us about as high a proportion of positive results as could be expected under the conditions. The spinal fluid, therefore, which shows evidence of neurosyphilis after the blood Wassermann reaction has become negative, is absolutely essential to the successful working out of the problem presented by late syphilis with gastric symptoms (Table III).

TABLE III.—INTERRELATION OF BLOOD AND SPINAL FLUID FINDINGS IN 177 PATIENTS WHO COMPLAINED OF "STOMACH TROUBLE".

Wassermann reaction on the blood positive; spinal fluid negative	41 (23 per cent)
Wassermann reaction on the blood negative; spinal fluid positive	72 (41 per cent)
Wassermann reaction on the blood positive; spinal fluid positive	32 (18 per cent)
Wassermann reaction on the blood negative; spinal fluid negative	32 (18 per cent)

32 PATIENTS WITH NORMAL BLOOD AND SPINAL FLUID WHO COMPLAINED OF "STOMACH TROUBLE".

Neurologic signs . . . . .	26
Vascular signs (aortic regurgitation and aortitis) . . . . .	2
Condition proved by therapeutic tests . . . . .	3
True gastric syphilis . . . . .	1

Again, it is apparent what an important role patients with negative Wassermann reactions on the blood and abnormal spinal fluids play in our work.

Few lessons are more important for the clinician who uses the examination of the spinal fluid as a diagnostic aid to learn than that a negative blood and a normal spinal fluid do not eliminate from the diagnosis the gastric crises of tabetic neurosyphilis. Of our 32 patients with normal bloods and spinal fluids 13 (40 per cent) had clinically typical gastric crises. Eleven of the 13 had definite neurologic signs of tabetic neurosyphilis. In the other 2 the diagnosis was based on the clinical course and history alone. While it is not within the scope of this paper to discuss the nature and location of the central lesion giving rise to the gastric crisis, we have been strongly impressed with the idea that in a considerable proportion of the cases, at least, the process involves the vagus, the



sympathetic mechanism, the splanchnic nerves, and the large abdominal ganglia rather than the cord.

**Gastric Findings as Such.** Having shown in a general way what the Wassermann reaction and the spinal fluid examination have contributed to clarifying the complaint of stomach trouble in 200 syphilitic patients, the results of the statistical compilation of the direct examination of these patients' stomachs may now be discussed. Test meals were given in 122 cases, and roentgenographic studies were made in 131 (Table IV).

TABLE IV.—TEST MEALS IN 122 SYPHILITIC PATIENTS WITH  
"STOMACH TROUBLE".

Normal acidity 40 to 60 . . . . .	47 (38 per cent)
Hyperacidity 60 and above . . . . .	14 (11 per cent)
Hypoacidity 40 and below . . . . .	61 (50 per cent)

ROENTGENOGRAPHIC FINDINGS IN 131 SYPHILITIC PATIENTS WITH  
"STOMACH TROUBLE".

Negative roentgenogram . . . . .	110 (84.0 per cent)
Duodenal ulcer . . . . .	11 ( 8.4 per cent)
Gastric syphilis . . . . .	4 ( 3.0 per cent)
Questionable pyloric lesions . . . . .	4 ( 3.0 per cent)
Cardiospasm . . . . .	1 ( 0.8 per cent)
Gastric ulcer . . . . .	1 ( 0.8 per cent)

Eusterman has directed attention to the hypoacidity of the stomach which is the seat of syphilitic lesions as such, so that this finding will not be discussed from the standpoint of its mechanism. Wile (quoting Neugebauer) found hypoacidity in 62 per cent of cases of early syphilis, but nothing characteristic in late syphilis, although a majority of cases tends toward hypoacidity.

It would seem that the routine roentgen-ray examination of syphilitics who complain of stomach trouble does not yield a large percentage of positive results. We make no attempt to discuss the details of these findings, which are covered by Eusterman's work on gastric syphilis (Table IV).

**The "Neuro" Group.** About 10 per cent of the 200 syphilitic patients who complained of stomach trouble had received a diagnosis of gastric neurosis, neurasthenia, functional disorder of the stomach and so forth, before complete studies of the case from the syphilologic standpoint were made. The diagnosis of latent syphilis was in some cases appended to that of neurosis when the evidence for syphilis from the general standpoint seemed especially strong (Table V).

TABLE V.—21 "NEUROTICS" WITH "STOMACH TROUBLE" WHO HAD  
SYPHILIS.

Wassermann reaction on the blood positive . . . . .	7
Wassermann reaction on the blood positive; spinal fluid positive . . . . .	4
Wassermann reaction on the blood negative; spinal fluid positive . . . . .	8
Wassermann reaction on the blood negative; spinal fluid negative; neu- rologic signs positive . . . . .	2

There is no more dangerous practice in general diagnostic medicine than to make a final diagnosis of neurosis in the presence of evidence of syphilis, without a full investigation. Half of the "neurotic" patients in our series had positive blood Wassermann reactions and more than half had positive spinal fluids. Every "neuro" deserves at least a Wassermann test, and if there is reasonable additional presumptive evidence of syphilis, an examination of the spinal fluid.

**True Gastric Syphilis.** Inasmuch as the scope of this paper is limited to the consideration of the complaint of stomach trouble, in its relation to the general problem of syphilologic diagnosis, we omit consideration of the cases of gastric syphilis which appear in our series.

**The Surgical Relation of Stomach Trouble to the Diagnosis of Syphilis.** The series of 200 patients included 35 on whom needless operations had been performed because of various aspects of syphilis, leading to the complaint of stomach trouble. Twenty-seven of these patients had been operated on elsewhere, and 8 after entering the Clinic. Five of the 35 had sustained two operations without relief, and we were even confronted with 1 who had sustained four operations without relief. It is evident that the problem of the patient with late syphilis with a visceral syndrome and a complaint which suggests something operable, is a serious one, both from the standpoint of the patient and of the surgeon who wishes to reduce his percentage of error to the lowest possible terms. We have not included in this group of patients operated on those whose definitely non-syphilitic lesions were diagnosed before operation, found, and removed at operation with relief of symptoms. Such operations must obviously be as frequent and necessary in the syphilitic patient as in the non-syphilitic. Our plea, however, is for a fuller recognition of the extraordinarily misleading influence of syphilis in the production of "operable complexes," and the usual futility of such operative interventions as are attempted without an adequate diagnostic study.

Table VI illustrates the fact that in almost none of the cases in our series was syphilis so entirely latent or occult that it could have been omitted reasonably from a complete diagnostic appraisal of the case.

In all but 2 of 35 cases, then, there was some clue available to direct the suspicion of the diagnostician and surgeon toward syphilis. The question of the advisability of operation in the presence of reasonable grounds for suspecting syphilis will be discussed.

In Table VI the patients subjected to operation are divided into two distinct types; in the first group, the symptoms of neurosyphilis were largely upper abdominal in character and led to operation for supposed gall-bladder conditions and gastric lesions. We may fairly say these operations were unnecessary, and would have been avoided had an intensive study of the case been made with reference

to syphilis, and a therapeutic test been carried out. On the other hand, the second group of patients presents a problem in which we believe the surgeon should have right of way over the syphilographer. One of us (Stokes) has proposed that when after a careful study the question of malignancy is raised in the face of a concomitant syphilis, the most important move is the surgical exploration, which will clinch the diagnosis and afford the patient the promptest and best prospect of relief. Table VI indicates that this issue is by no means theoretic, and that the diagnostician will not infrequently be obliged to call for exploration in the presence of symptoms suggesting visceral syphilis, but from which the possibility of operable malignancy can only be eliminated by exploration. We do not believe that there is any excuse for subjecting a patient who may have an operable malignant lesion to the delays of treatment for syphilis before operation.

TABLE VI.—SURGICAL EXPLORATIONS WITHOUT RELIEF ON 200 PATIENTS WITH SYPHILIS WHO COMPLAINED OF "STOMACH TROUBLE".

	One operation.	Two operations.	Three operations.	Four operations.
Patient admits early syphilis with definite physical signs . . . .	13	1	0	0
Patient denies early syphilis with definite physical signs . . . .	14	4	0	1
Patient admits early syphilis but without definite physical signs . .	2	0	0	0

35 PATIENTS WITH SYPHILIS WHO HAD BEEN OPERATED ON FOR "STOMACH TROUBLE" WITHOUT RELIEF.

Gastric crises in tabetic neurosyphilis . . . . .	11
Other types of neurosyphilis . . . . .	16
Gastric syphilis (question of malignancy) . . . . .	3
Hepatic syphilis (question of malignancy) . . . . .	3
Latent syphilis with gastric symptoms relieved by treatment . . .	2

As the obverse of this point of view, we submit the principle that patients with inoperable or presumptively inoperable abdominal malignant lesions, from whom a suspicion of syphilitic infection can be obtained, should be given the benefit of treatment for syphilis. It may further be advantageous to apply such tests to admittedly benign lesions of the abdominal viscera in which there is reason to suspect concomitant syphilis, before proceeding to operation. This should be especially true in gastric lesions in which an ulcer is recognizable, since syphilitic ulcer of the stomach is a well established entity, and the effect of gastro-enterostomy on a patient with a syphilitic ulcer is by no means as desirable as the resolution of the ulcer under treatment for syphilis.

Brief abstracts of a few of the cases in our series suggest some of the aspects which syphilis presents to the internist or surgeon who

is confronted with symptoms which seem to indicate the need for an exploratory or other operative interference.

CASE I (A350913).—Miss C. H., aged twenty-nine years, gave as her chief complaint "stomach distress." There was no history of syphilis. A palpable mass could be identified in the epigastrium. The test-meal showed marked hyp acidity, and the roentgenologist's report was inoperable carcinoma of the stomach. The blood Wassermann reaction was strongly positive; the spinal fluid negative. There was considerable cachexia. Inasmuch as the carcinoma of the stomach was considered inoperable, the patient was placed on treatment for syphilis and was given three injections of arsphenamin. The patient had not shown any appreciable improvement with the amount of treatment for syphilis and a reconsideration of the operative possibilities in the case then led to an exploration. An inoperable condition of the stomach was found, but tissue was removed and the pathologic report was: "Repeated examinations negative for carcinoma. Many giant cells. Syphilis?." The patient was unable to remain for further treatment for syphilis.

This case well illustrates the principle that operability should have the right of way over treatment for syphilis whenever surgeon and internist believe that an operable carcinoma is present with concomitant syphilis.

CASE II (A300769).—Mrs. F. M., aged thirty-one years, complained chiefly of nausea and vomiting. Physical examination was negative, except for slight pain in the region of the gall-bladder. No roentgenograms were taken. The blood Wassermann reaction was positive. A preoperative diagnosis of cholecystitis was made. On exploration the gall-bladder and appendix were found to be normal and were not removed. Treatment for syphilis was instituted with the prompt and complete disappearance of all symptoms.

CASE III (A129487).—Mr. J. F., aged thirty-six years, complained chiefly of stomach trouble. A history was obtained of probable syphilitic infection, but there were no definite neurologic signs. A clinical diagnosis of exophthalmic goiter was made, followed by ligation of the thyroid artery. Apparently as an afterthought a Wassermann test was made and found to be positive. After the resection of part of the thyroid the patient was sent home on mercury pills and potassium iodid and instructed to return later for thyroidectomy, the syphilis being apparently regarded as of too little importance for further consideration. Five years later the patient returned. He had sustained no relief whatever from the thyroidectomy and his stomach trouble was worse than at the time of his first examination. He now presented marked neurologic signs which made a diagnosis of tabetic neurosyphilis with gastric

crises unescapable. The blood Wassermann reaction and the spinal fluid examination were both negative. He declined to remain for treatment.

This type of case well illustrates the unfortunate results of ignoring the gravity of syphilis as a complication, and dismissing the patient with inadequate treatment, only to have late neurosyphilitic complications develop through neglect. Had adequate treatment been instituted when the positive blood Wassermann reaction was first found, the patient would have been none the worse for the diagnostic error at least.

CASE IV (A368057).—Mrs. A. B., aged fifty-three years, gave cancer of the stomach as her chief complaint. There was no history of syphilis. The gastric contents were examined. Roentgenograms of the stomach were not made. The blood Wassermann reaction was strongly positive. There was a palpable mass in the upper right abdomen. A preoperative diagnosis of pancreatic cyst was made and exploration was done without previous specific treatment. The stomach, pancreas, and gall-bladder were found to be normal. The liver was studded with "tumors." The pathologic report on one of these tumors was chronic hepatitis. After the operation specific treatment was instituted, and was followed by rapid and pronounced improvement.

So far as our observations on surgical intervention in the group of syphilitic patients under consideration are concerned, we are impressed with the fact that the surgeon and the diagnostician think much too seldom of syphilis as a factor in their work and, like the profession at large, are too easily satisfied with superficial and inconclusive evidence of its absence. In the phrase which one of us (Stokes) has often used, their "index of suspicion is too low." Very often even the blood Wassermann reaction is not invoked to assist in the diagnosis, and if it is, a single negative return seems to clear the field for operative intervention. It may be safely said that as long as internists and surgeons explore for chronic abdominal symptoms without a very serious reckoning with the possibility of syphilis in general, and neurosyphilis in particular, just so long will there be a liberal margin of diagnostic blunder in this field. Such a reckoning with syphilis, we are now learning, must not stop with the merely routine precaution of a Wassermann test on the blood, which in the very type of case in which operation is least desirable, is apt to be the most deceptive and inadequate of guides. The neurologic examination and the spinal fluid test will, if intelligently applied at the demand of a syphilologically suspicious and alert mind, greatly reduce the incidence of negative explorations in neurosyphilitic patients.

Moreover, unless confronted with an emergency, or with evidence strongly suggesting a malignant process, it is a mistake for the surgeon to ignore the positive Wassermann reaction in his patient before exploration. An examination of the spinal fluid has more than once disclosed in patients under consideration for operative intervention, a condition of affairs in distinct contraindication to surgery until the syphilis had been brought under control.

**Results of Treatment for Syphilis.** Not all the patients in whom a final diagnosis of syphilis was made, remained under our treatment for their syphilitic infections. Table VII shows the results in 109 patients who were treated with greater or less thoroughness. All patients whose improvement was slight or doubtful for any reason are eliminated, so that the results represent substantial benefit, amounting in many instances to complete arrest of the symptoms and a restoration to working efficiency.

TABLE VII.—THE EFFECT OF TREATMENT FOR SYPHILIS ON 109 SYPHILITIC PATIENTS COMPLAINING OF "STOMACH TROUBLE".

	Improved.	Not improved or indefinite.
Neurosyphilis in general . . . . .	51 (73 per cent)	19
Neurosyphilis, with neurologic signs only . .	6 (55 per cent)	5
Neurosyphilis, signs and positive spinal fluid .	41 (79 per cent)	12
Neurosyphilis, gastric crises of tabes dorsalis .	10 (62 per cent)	6
Latent syphilis, Wassermann reaction on the blood positive . . . . .	13 (67 per cent)	6
Therapeutic tests in gastric syphilis with a question of malignancy . . . . .	3 (100 per cent)	0

The average outlook for improvement following treatment for syphilis that may be expected in syphilitic patients who complain of stomach trouble is, then, approximately 70 per cent. Forty-three per cent of the 109 patients were considered to be very markedly improved and seemed in good condition. Thirty-five per cent showed some improvement and amelioration of symptoms. Twenty-three per cent failed to respond to treatment, or if there was response it was too indefinite to be considered beneficial. We shall make no attempt at this point to go into the complex questions of serologic versus clinical and symptomatic improvement in patients of this type. We call attention, however, to the really very presentable outlook for some degree of improvement in patients with gastric crises, whose notorious tradition of resistance to treatment forms one of the discouragements of syphilotherapy.

The therapeutic indications for each syphilitic patient with a gastric complaint must be judged, of course, on the merits of the case, and little can be expected of haphazard, slipshod, or inadequate treatment which does not meet the pathologic lesion underlying the patient's complaint. Case V, for example, illustrates the futility of following up a suspicion of syphilis with ineffective and partial treatment, not directed at the underlying condition.

CASE V (A87594).—Mr. F. H., aged thirty-four years, complained chiefly of vomiting spells. He gave a history of early syphilis. Physical examination was negative. A test meal showed hyperacidity; roentgenograms of the stomach were negative. Pupils were sluggish to light but not fixed. Serum Wassermann reaction was negative. A preoperative diagnosis of chronic cholecystitis and chronic appendicitis was made and verified at operation. Relief of symptoms did not follow the operation, however, and the patient was then given two injections of arsphenamine "on suspicion", but without appreciable result. Seven years after operation, he returned stating that he had had no relief from his symptoms. The blood Wassermann reaction at this time was again negative, but a spinal fluid examination showed positive evidence of syphilis of the nervous system. A diagnosis of tabetic neurosyphilis with gastric crises was made and systematic intensive treatment with arsphenamine and mercury resulted in striking improvement.

If, in view of his history of infection and sluggish pupils, a spinal fluid examination had been resorted to in the face of a negative Wassermann reaction at the time of operation, this patient's tabes could probably have been completely arrested. The two arsphenamine injections given to satisfy a feeling that something ought to be done for the suspected syphilis accomplished nothing for the patient, although the fact that his crises were amenable to treatment was subsequently demonstrated.

A patient who owes his gastric symptoms to syphilis of the nervous system requires not routine treatment, or treatment for gastric syphilis as such, but treatment for syphilis of the nervous system. To apply therapeutic methods, adapted to gastric syphilis, or to syphilis of the nervous system, with the prompt and vigorous use of arsphenamine as soon as the diagnosis is made, to a patient with syphilis of the cardiovascular system, would be exceedingly risky, not to say fatal. Proper controls in the form of examinations of the spinal fluid and the application of special methods, such as intraspinal treatment when indicated, are a part of the treatment of neurosyphilis with gastric symptoms. More transient improvement of subjective complaints under a routine amount of treatment by an inexperienced practitioner is not a substitute for the well planned system which aims to secure a permanent result.

We suggest as a matter of some interest, the possibly coincidental but from the symptomatic standpoint none the less striking improvement of patients with definitely recognizable gastric lesions of a non-syphilitic character, such as duodenal ulcer, which do not respond objectively to treatment for syphilis. This response suggests interesting speculations with regard to a possible neurotrophic origin for certain of these lesions in syphilitic patients. In our series were 8 cases of duodenal ulcer and 3 of gastric ulcer, all but 1 of which were diagnosed by the aid of roentgenograms and the history.

From a syphilologic standpoint, 6 were classified as latent syphilis, 1 as possible syphilitic gastric ulcer, and 4 as "neurosyphilis." In all, specific treatment was instituted and no particular attention was directed toward a definite ulcer regime. Two of the patients with duodenal ulcer came to operation before relief was obtained. In the remaining 9 cases, operations were not performed and all the patients were greatly relieved from their gastric symptoms, reporting "excellent", "85 per cent better", and "much better."

It is of course impossible to evaluate fairly the relative worth of the various diagnostic methods employed in our investigations of the meaning of stomach trouble in our group of 200 syphilitic patients with this complaint. It interested us, somewhat, however, to tabulate the proportion of positive results obtained in these patients by the various methods of objective clinical approach employed after they had entered the Clinic with their complaints of stomach trouble (Table VIII). It would obviously be unfair to give to such a procedure as the provocative test and Wassermann series employed in 10 cases, with positive results in 9, a higher rating than the spinal fluid employed, for example, in 177 cases.

TABLE VIII.—ROUGH ESTIMATION OF THE WORTH OF CERTAIN FORMS OF EXAMINATION IN TERMS OF POSITIVE RESULTS OBTAINED IN THE STUDY OF 200 SYPHILITIC PATIENTS WITH "STOMACH TROUBLE."

Procedure	Patients.	Positive results per cent.
Spinal-fluid examination . . . . .	177	59.0
Blood Wassermann tests . . . . .	200	45.5
Neurologic examination . . . . .	140	22.0 <sup>1</sup>
Roentgen-ray studies . . . . .	132	16.0 <sup>2</sup>
Provocative and Wassermann series . . . . .	10	90.0

<sup>1</sup> Includes only those with negative blood and spinal fluid and otherwise negative except for the neurologic signs.

<sup>2</sup> Findings of duodenal ulcer, gastric ulcer, etc., are included in this percentage.

This tabulation does not suggest to us so much the comparatively small yield, so to speak, from some of the procedures whose necessity cannot be denied, as it does the urgent need for an extension of current conceptions of what constitutes a proper clinical study of a patient with a gastric complaint who presents a reasonable suspicion of syphilis. What constitutes a reasonable clinical suspicion of syphilis has been all too little considered. It seems safe to say that clinicians and surgeons in general, to judge by the operative record of our cases, may allow themselves considerably more latitude in suspecting syphilis in patients with abdominal symptoms. Where grounds for suspicion are present, they should call for complete investigation of their cases by syphilologic methods before they proceed to a diagnosis or to treatment. We must contend perforce, from



the results of our study of this and other series of cases, that the single Wassermann test and a negative history of early manifestations cannot be regarded as synonymous with adequate syphilologic examination. They merely serve as guides to a more acute and penetrating suspiciousness of mind. That penetrating suspiciousness is coming to demand, more and more, a complete examination of the spinal fluid, with a neurologic study, before operation is resorted to in doubtful cases.

**Summary.** 1. Of 200 syphilitic patients who complained of stomach trouble, 70 per cent had neurosyphilis. 20 patients (10 per cent) had organic lesions (syphilitic or non-syphilitic) of the gastro-intestinal tract, 9 (5 per cent) had lesions of the heart, and only 4 per cent had true syphilis of the stomach.

2. The history of syphilitic infection is unreliable. Men give such a history three times as often as women. Sixty per cent of the men and 70 per cent of the women could not give histories of secondaries. Only two-thirds of those with histories of infection were diagnosed in the primary stage.

3. In only 36 per cent of the whole series of patients was syphilis recognized before they came to the Clinic.

4. The medical diagnoses made before their examination in the Clinic were apparently largely based on history (90 per cent) and blood Wassermann reaction (65 per cent). After examination in the Clinic the diagnoses were based most often on history (60 per cent), spinal fluid examination (59 per cent), and blood Wassermann reaction (44 per cent).

5. Only 10 per cent of the patients had had spinal fluid examinations before they entered the Clinic, yet 59 per cent were positive. The test deserves greater popularity.

6. Only 44 per cent of the patients gave Wassermann positive reactions on the blood when they entered the Clinic and 56 per cent gave negative reactions largely as a result of treatment elsewhere. The greater diagnostic importance of the spinal fluid examination is again suggested.

7. Seventy per cent of the patients with persistently Wassermann-negative bloods not due to treatment had positive spinal fluids.

8. Negative blood Wassermann and negative spinal fluid do not exclude neurosyphilis as a cause of gastric complaints. Of 32 such patients, 40 per cent had gastric crises with neurologic evidence of *tabes dorsalis*.

9. We suggest that the seat of the lesion in patients with gastric crises and negative spinal fluid examinations is in the vagus, the abdominal ganglia, and the sympathetic system.

10. Fifty per cent of 122 patients had hypoacidity and 38 per cent were normal. Hyperacidity was rare.

11. Of 132 patients having roentgen-ray examinations 84 per cent

were negative and only 6 per cent showed definite or doubtful syphilitic lesions.

12. "Gastric neurosis" and "functional stomach" are dangerous diagnoses, if any suggestion of syphilis is present. In 50 per cent of these cases blood Wassermann reactions were positive, and in more than 50 per cent the spinal fluids were positive.

13. Eighteen per cent of our patients with stomach trouble had had needless operations, 80 per cent before entering the Clinic. In all but 2 of 35 patients there were clues to the underlying syphilis, which were not followed up, or a negative blood Wassermann reaction that had been accepted as final, when other evidence of syphilis could have been found.

14. One-third of the needless laparotomies were on patients with gastric crises.

15. When the question of operable malignancy is raised, exploration should precede a therapeutic test for syphilis. If there is no reasonable probability of an operable malignancy being present, or if the lesion appears inoperable with syphilis present, treatment for syphilis should precede operation.

16. A general raising of the "index of suspicion" for syphilis, among internists and surgeons, would reduce operative mistakes in patients with abdominal symptoms. A blood Wassermann test is often insufficient to clarify the situation, but should at least be routine.

17. Surgeons should not ignore positive Wassermann reactions obtained before operation.

18. The results of treatment for syphilis in 109 cases in which patients remained for treatment were gratifying. Seventy per cent improved, 43 per cent were relieved of their complaint.

19. Treatment for syphilis underlying a gastric complaint must be directed according to the special indications in the case, and must not be merely general. Different methods will be required for underlying syphilis of the nervous system, the stomach, or the heart for example.

20. We observed striking symptomatic improvement in certain cases of gastric and duodenal ulcer in neurosyphilitic patients in whom the roentgen ray after treatment showed the lesions itself to be still present.

21. The spinal fluid examination stands out from this investigation as a procedure of the highest importance, outranking the serum Wassermann reaction in diagnostic syphilology as applied to internal medicine. Its wider use for diagnosis should be developed with proper facilities for its performance and control.

#### BIBLIOGRAPHY.

1. Cabot, R. C.: *Differential diagnosis*. 2 ed. Philadelphia, 1915, p. 253.
2. Carman, R. D.: Syphilis of the stomach in its roentgenologic aspects. *Am. Jour. Syph.*, 1917, 1, 111.

3. Eusterman, G. B.: Syphilis of the stomach, a report of forty cases. *Am. Jour. Syph.*, 1918, 2, 205.
4. Gennerich, W.: *Die Syphilis des Zentralnerven Systems*. Berlin, 1921, p. 100.
5. Stokes, J. H.: The problems of syphilis in general diagnosis. *Journal-Lancet*, 1920, 40, 457.
6. Stokes, J. H.: Principles underlying the therapeutic test for syphilis. *Med. Clin. North America*, 1921, 5, 486.
7. Wile, U. J.: Visceral syphilis. Syphilis of the stomach. *Arch. Dermat. and Syph.*, 1920, 1, 543.

## THE SAFEGUARDING OF THE TONSIL AND ADENOID OPERATION:

### THE PREVENTION AND TREATMENT OF SOME OF THE POST-OPERATIVE COMPLICATIONS OF THIS OPERATION.\*

BY GEORGE FETTEROLF, M.D.,

PHILADELPHIA, PA.

THE sequelæ of the tonsil and adenoid operation which will be discussed in this communication are the following:

1. Temperature elevation.
2. Increase of arthritic symptoms.
3. Edema of the palate and uvula.
4. Hemorrhage.
5. Middle-ear inflammation.
6. Acidosis.
7. Pulmonary abscess.

1. **Temperature Elevation.** This condition, frequently associated with a degree of tachycardia which is out of proportion to the pyrexia, is very often found. The height ranges from 99° to 101°, rarely going higher unless there is some definite focal lesion, such as an infected middle ear. It may last one day, rarely more than two, and is so common that it usually is unnecessary to attach any importance to it, with the exception that no patient with a mouth temperature of over 99.5° should be allowed to leave the hospital.

In order to get definite figures, I took the charts of 25 private patients consecutively operated upon at the University Hospital and averaged the temperature figures. I selected the highest recorded temperature the day of the operation, the day after the operation and the day following that. The following is the result:

On the day of operation the average high temperature was 98.6°.

\* Read before the Section of Otolaryngology and Laryngology of the College of Physicians of Philadelphia as part of a Symposium on "Safeguarding Tonsillectomy," December

On the day following operation the average high temperature was 99.3°.

On the second day following operation the average high temperature was 98.9°.

What the elements are which cause this elevation naturally are difficult to analyze. The local pain and discomfort, the general physical distress, the bronchial irritation from the ether may and probably do enter into it. It is likely that an important factor is the extra dose of tonsil-derived toxins which necessarily is squeezed into the circulation during manipulations essential to a tonsillectomy. With this probability in mind it follows that good elimination should be maintained during the early postoperative days, the bowels being kept open and plenty of water being imbibed. This last procedure is not a difficult one to follow, with exceptions, of course, if the water is taken in large, rapid gulps, instead of in widely separated sips or through a tube.

There is one type of temperature elevation which always is gratifying to the operator, and that is the one which follows severe hemorrhage, as it indicates the absence of or recovery from shock and also tells us that the blood-making apparatus is at work replacing the lost vital fluid.

Should the fever rise above 101° and remain there for two or more days it should be the signal for a thorough examination of the sinuses and ears and of the system in general, particularly the lungs, heart and kidneys. A blood count at such a time may afford a suggestion as to what is going wrong.

**2. Increase of Arthritic or Neuritic Symptoms.** When a patient has been operated upon for the purpose of removing a focus which has been causing an arthritis, a neuritis or some other such condition, a temporary exacerbation occasionally is seen postoperatively. Instead of this being regarded as a complication it is not unreasonable to view it as a confirmation, a confirmation of the diagnosis that the focus was in the tonsils. Such a viewpoint is consoling both to patient and operator. If the patient can be told that the operation itself naturally would cause an inordinate dose of tonsil poison to be forced into the system and that the increase of symptoms means that the diagnosis of tonsil responsibility is confirmed, then all fears are allayed.

A case which is apropos is mentioned by Keiper,<sup>1</sup> who states that he "had one case wherein after tonsillectomy a severe infection of the right knee-joint developed." The case is reported thus briefly, but it indeed would have been interesting to know whether or not the organisms in tonsil and knee were the same. This case is of interest also in connection with the question of the method of transmission of the infection in cases of pulmonary abscess.

<sup>1</sup> The Tonsil Question Up to Date, Laryngoscope, St. Louis, 1921, 31, 777.

3. **Edema of the Palate and Uvula.** This occurs in varying degrees, and while it sometimes is found in children it is far more frequent in adults. In my experience it is more likely to occur when the patient has had a similar condition during antecedent attacks of tonsillitis or quinsy, when there is a large upper tonsil pole, when the tonsil is adherent to its fossa wall or when some of the mucosa of the soft palate overlying the palatoglossus has been lifted from the underlying tissue during the freeing of the upper half of the tonsil from its bed. A curious feature of this edema is that the posterior portion of the uvula is usually more swollen than is the anterior. Unless the anterior mucosa and submucosa have become toughened by food friction, and therefore swell less readily, only a detailed study of the venous and lymphatic systems will give us a true explanation of this phenomenon.

The condition always is a distressing one and not infrequently it causes alarm to the patient by creating fears of strangulation. It also prolongs convalescence, since it adds tremendously to the ordinary difficulty in swallowing, not only by narrowing the pharynx, but in addition the lengthened uvula extends so far down that it becomes part of the food bolus and the patient tries to swallow his own uvula. This is a powerful discourager to eating and is altogether very annoying. When it is extreme the nutrition of the uvula may be slightly interfered with, and I fancy that all of us have seen a spot of necrotic epithelium at the tip of the uvula in some of these cases.

There is nothing which will give to this condition any relief worthy of the name. As it really is a hypostatic condition (with possibly at times an element of infection added) it is irrational to expect that any local application will afford relief. Punctures are recommended, but the effect of these is slight or nil, and such incisions never reach the most swollen part, viz., the posterior part. As they always close in a brief time it is difficult to believe, on either theoretical or practical grounds, that they avail anything. And, on the basis that the condition is due to a severing or constriction of the effluent venous and lymphatic pathways, it is best to realize that the gradual disappearance of pressure or the establishing of collateral paths must be awaited with as much philosophic anticipation as patient and physician can command.

In the early days of my practice I had a case in which the edema was extreme and caused intense discomfort to the patient. Feeling that I had to do something I slipped a lingual tonsillotome over the enormously lengthened uvula and cut off the lower half. This gave no relief whatsoever, and to add insult to injury, when the palate healed it did so in the form of an inverted  $\Delta$ , there being a distinct notch where the uvula had been. No unpleasant consequences resulted, but this taught me two things: Never to do

it again and that the edematous uvula is not all uvula. Approximately half of it is uvula, viz., the lower half, and the other half, viz., the upper half, soft palate.

An aggravation of this condition is found when the uvula is bifid, as under these conditions the lower end becomes club-shaped and may swell enormously.

Various applications have been recommended for local use, tannic acid, tincture of benzoin, silver nitrate solution, adrenalin chloride solution, etc. Sometimes comfort can be given the patient by having him lie on his side, and this frequently will check gagging. Ice may be used externally and in the mouth, but altogether it is a painful condition and a trying one, and only Nature's methods will give ultimate relief.

4. **Hemorrhage.** This is the most important phase of tonsil operative work. There are two phases to the situation, the preventive and the curative, and of these two the preventive is the more important.

It is not putting the case too strongly to say that no patient should be submitted to a tonsil and adenoid operation whose bleeding habits have not been gone into thoroughly and whose coagulation and bleeding time have not been taken preoperatively whenever this is practicable. In addition, it should be axiomatic that no patient should leave the operating table until all bleeding has ceased, this to be proved by careful inspection.

In the present stage of our tonsil technic the phrase "bloodless tonsil operation" should be abolished from usage unless we are using the words in a Pickwickian sense. "Bloodless" means without blood, and this word will be applicable only when someone is able to develop a method of operating which invariably sheds no blood at the operation and which invariably is followed by no postoperative hemorrhage. At the hands of all of us some cases are operated on with but a few drops of blood being lost, and in others the amount of bleeding, even if but brief, is at times terrifying. Again in some cases the bleeding is negligible at operation but alarming secondarily.

The question of hemorrhage at operation ordinarily need not cut any great figure if the operation is performed with deliberate care, attended by thoroughness and assured technic. A complete removal of the tonsil, followed by gauze pressure in the tonsil fossa, using any astringent the operator finds most serviceable (my own preference is for 10 per cent solution of silver nitrate) and the picking up and ligating of all bleeding-points, affords the least chance for prolonged bleeding on the table and the greatest insurance against postoperative trouble. For many years I have tied off every bleeding-point, since experience (and I fancy that all will agree with this) has shown that the tiny bleeding-point of two o'clock in the afternoon may become the gusher of midnight.

I use the ordinary Kelly hemostat, for the reasons that it has a broad point, thus making the closing of the knot easy, and the curve is of value in depressing the tongue or retracting the anterior pillar. I use no needle, simply a surface tie, employing No. 2 chromic catgut, softened in water, for the purpose. I never have found any knot-tying device necessary, the fingers being all sufficient for the purpose. In this connection it should be stated that we may be compelled to modify the freedom with which suture ligatures are used in the tonsil fossa. It is at least conceivable that septic material may thus be introduced into the tissues of the pharynx and that septic thrombi may be formed later to cause trouble elsewhere in the body.

The bleeding may come from anywhere in the fossa, and the greater one's experience the more certain does one become of this. The three most difficult places in which to find and clamp a bleeding vessel are high up in tonsil fossa, low down in the fossa and on the posterior surface of the anterior pillar. A few points about these: three times have I had great difficulty in securing vessels in the upper part of the fossa. In the first case of this kind, after twice securing the vessel with a hemostat and then having the ligature cut completely through the tissues, I passed a large, strong, curved needle through the palate, entering mesially to the fossa and emerging laterally to the anterior pillar. This secured the vessel, but the patient six weeks later died of pulmonary abscess, this being the one tonsillectomy case I have lost.

In all of them with one blade of a pair of scissors in the tonsil fossa and one anterior to the palate I cut through the anterior palatine arch to the upper pole of the fossa and then had no difficulty in getting the offending vessel. An interesting feature of these cases is that the arch on the cut side healed symmetrically with the other.

In a number of cases a very annoying feature has been the slow and repeated filling of the tonsil fossa with blood, apparently from below, and with no bleeding vessel discernible. Up to six years ago I habitually sewed a gauze pad into the fossa in such cases. At the time mentioned the thought occurred to me that one hitherto unexamined region was the posterior surface of the anterior pillar. With this idea in mind, at the next case presenting this feature I clamped with a hemostat and everted the anterior pillar, and on its posterior surface the offending vessel was found. In only 1 case since then has it been necessary to sew in a plug and in 6 others have I found a bleeding vessel situated at this place, where it easily was secured and tied.

It seems hardly reasonable to condemn the suction apparatus as a cause of immoderate bleeding. Its value as a cleanser of the throat is unquestioned and no one who uses it intelligently puts the end on the raw surface and sucks away. Its proper places

of use are in the cheek, in the pharynx and in the tonsil fossa, too, but in the last-mentioned place very gently and but momentarily. For the minor cleansing and in looking for bleeding-points gauze sponges sometimes are more efficacious. The complaint of the anesthetist that the suction motor sucks away his cherished ether is probably well founded, but in spite of this I question whether, weighing every actual advantage against every suppositious or proved disadvantage, any operator who has become accustomed to the apparatus ever feels quite at home, quite as efficient and quite as safe without it.

Secondary bleeding should be handled precisely on the same principles as in bleeding at operation. Two very important precautions are these: On returning the patient to bed to place him in a ventrolateral position with the face down and to have constant watching by a skilled nurse until the patient is out of ether. Should hemorrhage start the operator should be notified at once and should visit the case immediately. The handling of such a hemorrhage is no job for an intern and patients have died because the chief had been notified too late. A full dose of morphin should be given at once to an adult. Pressure with the operator's favorite styptic should be tried, and if this fails, every effort should be made to secure the vessel or vessels. If the patient, child or adult, is so unruly or the reflexes are so active that accurate work is impossible, there should be no hesitation in promptly (with the accent on the *promptly*) taking the patient to the operating room, reëtherizing and handling the situation in a truly surgical way. Great exsanguination is no contraindication to giving ether, as it is astonishing how the general condition improves under the anesthetic and how the pulse improves when the leak in the circulatory system is plugged. Refilling of the partly emptied vessels should be done with cautious deliberation, Murphy drip or small repeated enemas of physiologic salt solution being used to an amount which will not too suddenly increase the blood-pressure.

**5. Middle-ear Inflammation.** That an acute otitis media sometimes, although rarely, follows a tonsil and adenoid operation is not remarkable, but that it does not follow more frequently is remarkable. There are many factors which could predispose to this accident. Among these are the normally germ-laden condition of the upper respiratory tract, the trauma that is exerted upon the walls of the nasopharynx, the irritation of the nose and nasopharynx by the ether vapor and the presence in the nose and nasopharynx of clotted blood which quite easily could obstruct the tube or could be blown or coughed into it. It is impossible to decide which is the more dangerous, to leave the clotted blood in the nose and nasopharynx or to wash it out before the patient leaves the table. Many good and ultracareful operators use the latter procedure, have used it for years and favor it highly. I



confess to a slight feeling of trepidation when I see it done, as to me it carries with it the well-known dangers attending the use of the nasal douche. My own practice is to use postoperatively no spray or douche in the nose, and no case of middle-ear abscess has ever resulted from operation. Probably I have been fortunate but this experience has caused adherence to the let-alone principle.

As already remarked in substance, we always are operating in a septic field. In addition we always are operating upon septic tissue, and this probably is as true of the adenoid tissue as of the tonsils. The former growth hangs down in the nasopharynx usually in three, four or five leaflets, and it is quite astonishing to note how frequently in the rhinoscopic mirror we can see pus exuding from the fissures between these folds. I recall one curious case in which the growth was removed with the largest-sized La Force adenotome, and on opening the box to shake out the adenoid nearly a dram of yellow, creamy pus was found in the instrument with the severed adenoid. As no pain in the pharyngeal vault had been complained of, we evidently had here a chronic abscess of the adenoid.

Since the above was written there has appeared in the *Journal of the American Medical Association*, of December 17, 1921, a "Current Comment"<sup>2</sup> referring to some recent work along this line. The following is an extract and is of great practical interest:

"Heretofore the tonsils and the pharynx in general have received most of the consideration devoted to the bacteriology of the upper respiratory passages. Recently, however, a group of investigators at the University of Illinois College of Medicine devoted their attention to the adenoids. Cultures were taken from the excised adenoids to determine more definitely the flora of the nasopharynx. *Pathogenic bacteria were found in every specimen.* Of the more important organisms, hemolytic streptococci occurred in 61 per cent, pneumococci in 65 per cent, *Bacillus influenzae* in 40.9 per cent and *Bacillus diphtheriae* in 12 per cent. Other streptococci, diphtheroids, staphylococci, Gram-negative cocci, *Bacillus mucosus capsulatus* and *Bacillus fusiformis* were encountered. The depths between the folds and bottoms of the crypt like structures of the adenoids harbored hemolytic streptococci, pneumococci, and *Bacillus influenzae* in larger numbers than the epithelial surface or the nasopharyngeal swabs. The adenoids then, like the tonsils, are to be regarded as common foci harboring dangerous microorganisms."

Rarely though tubotympanic complications occur, when they do they may extend in any one of their favorite directions, and it behooves us to exercise every care to prevent and to recognize early such a complication. In the line of prevention as much

<sup>2</sup> Bacteriology of the Adenoids, *Jour. Am. Med. Assn.*, December 17, 1921, 77, 1975.

care in asepsis should be taken as in any other major operation, this including gloves, face mask and all other essential details. If there is to be a series of tonsil operations the operator, the assistants and the whole operating room paraphernalia should be just as aseptic for the second and subsequent operations as for the first. Even at this day one can see a series of operations performed without any of the staff changing gowns, with a perfunctory resterilization of instruments and with no change of the instrument table layout. This is all wrong. The punctilious attention to the details of surgical cleanliness at each individual operation takes time, but that much is due the patient. Only by following such a plan could an operator's conscience be clear if any serious complications should follow an operation. In case a patient should develop postoperative sepsis when the operator had failed to exercise all the niceties of aseptic technic, no matter at what cost of time or effort, the surgeon could not hold himself blameless, nor, in case the patient's people should become antagonistic and institute legal proceedings, could any brother surgeon testify wholeheartedly in his favor.

Another point is this: We all are familiar with the reflex otalgia which so frequently is complained of during the first few post-operative days. The glossopharyngeal nerve, with its pharyngeal and tympanic branches, as well as the vagus with its pharyngeal and auricular branches, afford a ready explanation of this phenomenon. So common is this that we can almost expect it. Yet not only is it the safest of practice always to examine the ears when such complaint is made, but it is advisable to go still further and practice examination of the ears as a routine procedure. Should a surgeon, for example, have one middle-ear abscess in 500 cases, it is only one-fifth of 1 per cent for him, and that may not be a high percentage for the operator, but to the patient and to that patient's family it is 100 per cent and a very serious matter.

6. **Acidosis.** The theory of this condition was first promulgated in 1850 and the present name applied in 1906. Medical literature is teeming with articles on this subject. The first one which directed the attention of laryngologists to the subject was presented by George B. Wood<sup>3</sup> in 1917. Two recent articles of interest are by Donnelly<sup>4</sup> on the "History of Acidosis," and by Farrar<sup>5</sup> on "Acidosis in Surgery: Its Occurrence during Operation and its Treatment by Glucose and Gum Acacia Given Intravenously." Farrar's article will be freely quoted in this communication.

The bicarbonates of the blood are carriers of the acid by-products

<sup>3</sup> Bicarbonate of Soda in Ether Anesthesia, Transactions of the American Laryngological Association, 1917, 39, 239.

<sup>4</sup> History of Acidosis, New York Med. Jour., August 21, 1920, 112, 246.

<sup>5</sup> Acidosis in Surgery: Its Occurrence during Operation and its Treatment by Glucose and Gum Acacia Given Intravenously, Surg., Gynec. and Obst., April, 1921, 32, 328.

of metabolism to the alveoli of the lungs and constitute the alkali reserve of the body. If the bicarbonates are present in the blood in large amount their ability to unite with the  $\text{CO}_2$  is quantitatively high, but if there is a diminution of the bicarbonates the  $\text{CO}_2$  will accumulate in the tissues. The resulting increased  $\text{CO}_2$  tension in the blood will stimulate the respiratory center to increased respiration. If alveolar ventilation is not then obtained a condition of intracellular acidosis results, with serious disturbance to internal (tissue) respiration.

Two things should be remembered as being of great importance: One is that carbohydrates and fats are base-forming foods and the other has just been mentioned, viz., that the bicarbonates of the blood are carriers of the acid by-products of metabolism to the lungs. Hence the necessity of avoiding proteid food and of administering bicarbonates before operation as well as afterward if vomiting appears.

The percentage of blood bicarbonates is an important factor in surgery for the reason that during operation, owing to increase in acid metabolism and to the fact that ether affects the liver, which is the regulator of acid by-products, there is considerable drop in the alkali reserve. As long as there are fixed bases in the blood the elimination of  $\text{CO}_2$  will continue. If the alkali reserve is high to begin with the drop may not be great enough to cause a severe acidosis.

"The more marked the existing acidosis to begin with the more sensitive is the patient to operative procedures, and the more likely is he to be let down by them into a region of danger.

"The essential feature in one's conception of acidosis is a general impoverishment of the blood in bases or in substitutes which generally give rise to bases, so that the body as a whole shows some systemic abnormality. If metabolism is faulty then there may be an accumulation of acid by-products in the body due either to excessive production or to defective elimination, or both together, and the condition of acidosis results."

Among Farrar's<sup>6</sup> conclusions are the following:

"The alkali reserve (bicarbonates of the blood) is the criterion of the acid-base balance of the body.

"Acidosis is a term used to signify an impoverishment of the blood in bases.

"The range of the carbon dioxide combining power of the blood in women (150 cases) . . . is about eight points lower than Van Slyke found for men.

"As the range is shorter in women the danger line is sooner reached, which accounts for the greater frequency of acidosis following operations in women than in men.

"The fall in alkali reserve during operation depends not only upon the anesthetic and the duration of the operation but upon the nature of the operation and the occurrence of hemorrhage and shock.

"The fall in the alkali reserve bears a close relation to the fall in blood-pressure and pulse-pressure. If the fall in blood-pressure is prevented there is a saving in alkali reserve.

"Carbohydrate feeding before and after the operation together with the use of bicarbonate of soda will do much to prevent or lessen acidosis."

Prevention of this condition is most important, and since I routinely have fed sodium bicarbonate to all patients before operation under general anesthesia I have had no marked cases. Vomiting has been absent or at a minimum and operative convalescence much more comfortable. As Wood<sup>7</sup> said in the paper mentioned above, "As a rule patients who have been given sodium bicarbonate before the operation, after having emptied their stomachs of the blood and fluid swallowed during the operation, do not vomit again and seldom complain of nausea, unless there is continued bleeding."

Should persistent vomiting occur after operation in the absence of any such obvious cause as continued hemorrhage, and should examination of the urine reveal acetone, treatment should be instituted at once. If food can be retained at all it should consist of carbohydrates and fat and not of proteids. Alkalies, bicarbonate of soda or, as suggested by Lynch,<sup>8</sup> citrate of soda as of more agreeable taste, should be given by mouth. Sodium bicarbonate (2 per cent) or glucose (5 to 20 per cent) should be given in small, repeated enemas or by Murphy drip. Lynch, who practises in New Orleans, states that the condition is much more frequent in hot weather and also that the postoperative use of codein and morphin tends to increase the quantity of acetone and consequently the incidence of vomiting. Before hearing this statement I had made no such observations, nor since using sodium bicarbonate routinely before operation, and morphin, heroin or codein in adults and paregoric in children after operation, when pain requires it, acidosis has occurred.

Van Slyke<sup>9</sup> in a recent communication stresses the importance of hemoglobin in this condition. He states that "the carriers of carbon dioxide may be most simply described as substances which hold in combination alkali, of which they supply CO<sub>2</sub>, as it enters the blood, sufficient to bind nearly all of it as alkali bicarbonate. . . The chief carbon dioxide carrier of the blood

<sup>7</sup> Loc. cit.

<sup>8</sup> Discussion of Paper by George B. Wood, see ante.

<sup>9</sup> The Carbon Dioxide Carriers of the Blood, *Physiol. Rev.*, January, 1921, 1, 141.

is the hemoglobin," it furnishing 80 per cent to 95 per cent of the alkali which neutralizes the  $\text{CO}_2$ .

7. **Pulmonary Abscess.** 80 per cent of postoperative cases of abscess of the lung are secondary to tonsil removal. In every 781 cases of tonsillectomy there is one which develops lung abscess. Rather startling statistics! The first figure is given by Wessler<sup>10</sup> who studied 100 cases of suppurative lung disease. Of the 100, 26 were postoperative, and of these 26, 21 were posttonsillectomy. The other figure is given by Keiper,<sup>11</sup> but he does not mention the sources from which his statistics are derived.

None of us know how many of our tonsil cases have been followed by this complication, particularly in our ward cases. They may not associate their pulmonary trouble with the antecedent operation and are likely to consult some other physician or clinic. An illustration of this is found in the report of Fisher and Cohen<sup>12</sup> of 5 cases, all of which had had tonsil operations in a hospital other than that in which they finally landed.

Richardson<sup>13</sup> first brought this matter to our attention in 1912. In this report he details the histories of two cases, both of which recovered, one after incision and drainage of the abscess and the other without any active interference. He described them as cases of "septic infarct of the lung."

Following this pioneer report a large number of observers have placed their cases on record. The *Quarterly Cumulative Index* for the first nine months of 1921 lists 13 articles on lung abscess, 5 of which relate to this condition as secondary to tonsillectomy. For 1920 there were 19 lung abscess papers, 4 of which were confined to the posttonsillectomy feature. In 1919 the figures were 15 and 1, and in 1918, 11 and 3. These numbers show the increasing attention which is being given to this subject.

Of all the sequelæ of tonsillectomy this is one presenting the highest percentage of fatalities; the death-rate varies, according to treatment, from 25 per cent to 50 per cent. It is therefore a condition toward which all possible prevention should be exerted, whose appearance should be constantly watched for and against which treatment promptly and intelligently should be directed.

The etiology of lung abscess has caused much discussion. Some favor inhalation as the main cause, while others believe that the process usually is an embolic one. Hedblom<sup>14</sup> states that the abscess is a sequel of inflammation, or results from infection reaching the lung tissue by way of the bronchus, the blood stream or

<sup>10</sup> Am. Jour. Roentgenol., April, 1919, 6, 161.

<sup>11</sup> Loc. cit.

<sup>12</sup> Pulmonary Abscess in Adults Following Tonsillectomy under General Anesthesia, Jour. Am. Med. Assn., 1921, 77, 1313.

<sup>13</sup> Tonsillectomy, with Consideration of its Complications, Washington Medical Annals, May, 1912, 11, 85.

<sup>14</sup> Pulmonary Suppuration, Med. Rec., September 13, 1919, 96, 441.

by direct extension. This, of course, covers the possibilities, and probably is as far as we can go.

Opinions vary greatly as to the effect of posture on the incidence of this disease. Wessler and Schwartz<sup>15</sup> state that "in those cases following operation the disease is usually seated in the upper lobes, while, on the other hand, abscesses resulting from the aspiration of foreign bodies and the chronic bronchopneumonia type of bronchiectasis usually localize in the lower lobes. The authors suggest that it is not improbable that the recumbent position during operation has some bearing on the upper lobe localization of these abscesses."

As opposed to this view, Richardson<sup>16</sup> believes that the head should be kept low and well extended. On the other hand it is largely the custom in New England for tonsil operations to be performed with the patient in the sitting position. This naturally would cast doubt upon the efficacy or necessity of the lowered head position, and leaves the question of operation posture a rather open one.

It has been stated<sup>17</sup> that the question of which pathway, circulatory or respiratory, transmits the infection to the lung is largely an academic one. While this may be true to some extent it does not alter the fact that every endeavor should be made to prevent, as far as possible, the ingress of blood, etc., into the trachea and bronchi during operations. To aid in keeping the lungs safe from abscess and other postoperative complications various suggestions have been made. These include posture (the head low and well extended), having the patient not too deeply under the anesthetic, warm ether, keeping the pharynx as clean as we can with suction apparatus, the abolition of motor-driven anesthetic apparatus and seeing that the patient is in proper condition for the operation. Some of these are and all of them may be of value and they suggest a few thoughts for brief elaboration.

Posture has just been mentioned.

That the motor-driven ether can force the pharyngeal contents into the trachea and bronchi would at least seem to be open to question. But to prevent too deep anesthesia always has seemed to me to be a tremendous desideratum. The coughing reflex is one of great value, and particularly when the patient has been returned to bed is it of importance that the pharyngeal reflexes return as soon as possible. Cases of deep narcosis have occurred in which the patients have bled into the stomach almost to the point of exsanguination without any swallowing movements being visible, the blood having trickled down the relaxed esophagus.

<sup>15</sup> Quoted by O. H. P. Pepper, *Prog. Med.*, September, 1921, p. 89.

<sup>16</sup> Discussion of paper by Fisher and Cohen, *Jour. Am. Med. Assn.*, October 22, 1921, 77, 1313.

<sup>17</sup> *Loc. cit.*

The same thing might easily happen to the trachea. The almost universal use nowadays of the prone position of the patient post-operatively is a great safeguard against such untoward and sometimes fatal happenings.

It would seem that the ideal degree of anesthesia would be to keep the patient just over the edge of absent reflexes, with the idea of thus helping to keep the tracheobronchial passages as clear as possible. In a series of cases in which there was used a motor-driven ether pump there occurred in a short time so many cases of deep cyanosis and real ether poisoning, several requiring oxygen and artificial respiration, that I soon gave it up. A trying feature was that the patients went to the bad so quickly that no warning was given. I might add that physicians experienced in anesthesia were presiding over the ether. Ether vapor pumped by a hand bulb with constant watching of the patient is quite safe, and in quantity and effect can be gauged with great accuracy, thus preventing too profound anesthesia and the entrance of blood, etc., into the trachea and bronchi.

Probably all believe that the suction apparatus is of value in preventing inhalation troubles. That blood and septic tonsil crypt contents do sometimes get into the trachea cannot be questioned. We frequently, in evidence of this, hear large tracheal rales, and often during operation we can see accumulations of blood, etc., appear in the pharynx during expiration and disappear downward during inspiration. It is here that suction is of great value, for such collections promptly can be drawn out. Richards<sup>18</sup> has suggested that the suction nozzle be used to pick up the masses squeezed out from the tonsil at operation, an idea which would seem to be worthy of adoption.

Voorhees<sup>19</sup> also favors this scheme. He believes that the possible inspiratory causes are blood-clots, pieces of adenoid, cheesy masses from the tonsil, a broken tooth or rarely pieces of tonsil which have broken off from the main mass in the removal. He states what is undoubtedly true, that "in using the Sluder method cheesy masses are forced out of the crypts during the engaging of the tonsil in the ring of the instrument." This would apply to any method of operating, but probably with greater force to one of the guillotine type than to the dissection method. Voorhees suggests that all cheesy masses and detritus should be removed from the tonsil crypts before the operation is begun.

It should not be forgotten that an actual foreign body, such as a loose tooth, an especially common condition in children during the years of their second dentition, may be the cause of the trouble. A corollary of this is that teeth which readily could be

<sup>18</sup> Discussion of paper by Fisher and Cohen, *vide ante*.

<sup>19</sup> Lung Abscess Following Tonsillectomy, Report of a Case with Bronchoscopic and X-ray Findings, *Laryngoscope*, August, 1921, 31, 609.

uprooted by a mouth-gag should be looked for before operation. I never will forget, at one operation, on picking out a white mass from the hollow of the cheek to find that it was a deciduous molar tooth which had come loose during the operation.

At present we are at sea as regards knowing the frequency with which lung abscess follows tonsillectomy under local anesthesia. Search of the literature has resulted in finding but two articles on this question. Porter reports 2 cases, as also do Simpson and Noah.

Porter<sup>20</sup> takes a very reasonable position. He says: "There exists a complicated network of veins, the plexus tonsillaris and the plexus pharyngeus, which cover the outer walls of the pharynx and the tonsillar cavities, receiving blood from the tonsils, tonsillar pillars and pharyngeal walls. These vessels are exposed and always injured even in the gentlest operative work. This too, is a field impossible to protect from germ-laden saliva and pus. It is therefore not difficult to believe that infected emboli could be dislodged from veins thrombotic from trauma and infection located in an area active in every attempt at speech and swallowing. I feel that there can be no doubt that infected emboli travel direct to the lungs and cause certain cases of pulmonary abscess. 'Aspiration' could not account for a brain abscess secondary to operation on the faucial tonsils, yet undoubted cases have been reported by careful observers." Such an embolic process naturally could occur under any form of anesthesia.

Simpson and Noah<sup>21</sup> state: "The writers believe that aspiration does not account for the production of lung abscess in the 2 cases reported. On the other hand they believe the following points favor hematogenous infection as the cause: (1) Both cases were operated on under local anesthesia in the upright position. (2) The mouths and throats were in a septic condition before and for some time after operation. In Case 1 considerable sloughing of the right tonsillar fossa and posterior pillar occurred. (3) Late occurrence of symptoms point to a blood-stream infection. (4) The occurrence of the abscess at the site of the tuberculous lesion, which was in both cases in the upper and middle lobes.

"Conclusions. 1. During or following operation septic material enters the veins, passes through the right heart to the lungs and there finds, in the presence of a tuberculous lesion, suitable soil for the production of an abscess.

2. "The possibility of aspiration of infected material as a cause of pulmonary abscess is not to be denied, yet we believe that more cases occur as a result of hematogenous infection than is generally supposed."

<sup>20</sup> Pulmonary Abscess Following Tonsillectomy under Local Anesthesia, Virginia Medical Monthly, March, 1921, 47, 12, 606.

<sup>21</sup> Report of Two Cases of Lung Abscess Following Tonsillectomy under Local Anesthesia in Tubercular Subjects, Penn. Med. Jour., March, 1920, 49, 322.



It should be added that both the cases reported by Porter "presented physical and roentgen-ray findings of definite lesions indicative of coexisting tuberculous pathology." While a local anesthetic is the one of choice for tonsillectomy in a tuberculous patient, these cases should help us to realize that the procedure is not without danger.

The onset of pulmonary abscess is usually quite characteristic, and when the following symptoms appear the chest should be carefully examined, preferably by a skilled internist: Persistence of an irregular temperature of 100° or more for several days; breath more foul than that usually found after tonsillectomy; chills, sweats, a feeling (frequently localized) of fulness or pain (the latter especially if the pleura is involved) in the chest; hemoptysis, which sometimes may be traced to the lungs by laryngeal examination, and an increase of leucocytes. Along with this there may be a feeling of anxiety and a septic appearance on the part of the patient. Later will come the purulent sputum, possibly blood-streaked, the diagnosis finally being confirmed by the physical signs and roentgen-ray and fluoroscopic examination. Norris and Landis<sup>22</sup> state that the diagnosis is rarely made prior to or in the absence of the sudden expectoration of a large quantity of purulent sputum. This should not be the case in posttonsillectomy abscess, for we should be on the lookout for the condition.

Occasionally the symptoms are atypical and misleading, as in the case reported by Hare and related later in this paper.

The symptomatology of this condition in children is described as follows by Wessler and Schwartz:<sup>23</sup> "Immediately or several days after the operation a distressing, persistent cough develops. This is especially harassing at night, but it may also be present during the day. With the cough there is usually a rise of temperature. This temperature is fairly constant during the first weeks, with minor fluctuations. Later it may become intermittent and there may be entire absence of temperature elevation for days. The physical signs of lung involvement are usually slight or absent during the early stages. Later, they may become definite and the evidences of a cavity may be made out. This is in contradistinction to the adult cases in which the physical signs, even of an extensive process and a large cavity, are usually indefinite.

"On the thirteenth or fourteenth day signs of gangrene are noted; including fetid breath, putrid sputum and hemoptysis. The sputum is then profuse. Club-fingers appear very early and disappear after the abscess has healed, sometimes earlier.

"During the course of the disease, complications such as perforation into the pleura with a resulting empyema or pyopneu-

<sup>22</sup> Diseases of the Chest and the Principles of Physical Diagnosis, 1917, p. 458.

<sup>23</sup> Am. Jour. Dis. of Children, 1920, 19, 137.

mothorax, severe hemoptysis or cerebral abscess, may make their appearance."

Norris and Landis<sup>24</sup> describe the sputum as follows: "It is negative for tubercle bacilli. The presence of elastic tissue points very strongly toward the presence of a pulmonary abscess. Its absence, however, does not rule out the presence of an abscess. By pouring the sputum on a piece of glass with a black background pieces of lung tissue may be picked out. The elastic tissue appears as grayish-yellow spots which are selected for examination under the microscope. If there is no microscopic evidence of broken-down lung tissue the sputum should be stained with one of the elastic-tissue stains, such as Weigert's."

The death-rate in lung abscess is very high. Fisher and Cohen<sup>25</sup> report 5 cases with death in 3 and chronic invalidism in the other 2. Walker<sup>26</sup> collected 132 cases, with a death-rate under medical treatment of 54 per cent and with a surgical mortality of approximately 25 per cent. Obviously the disease is largely a surgical one, a conclusion reached by Norris and Landis,<sup>27</sup> who as the result of a study of 30 such cases state that the mortality statistics of lung abscess "make imperative the constant coöperation of a surgeon in all such cases."

Hare<sup>28</sup> relates an interesting case in which the symptoms were such as to suggest an exploratory abdominal section for the purpose of studying the condition of the gall-bladder, the appendix and the right kidney. This was not done, however, and eventually pulmonary signs, including the usual foul expectoration, cleared the diagnosis. The patient did so well under no treatment whatsoever directed toward the abscess that she was discharged from the hospital. Later the condition recurred and the patient became so ill that operation was performed, consisting of incision, drainage and the use of Dakin's solution. Gradual but complete recovery ensued.

Another interesting case is described by Lilienthal.<sup>29</sup> The first symptoms suggesting abscess appeared about a week after operation. Six weeks after operation there was a pulmonary hemorrhage and during the next few weeks there were fifteen hemorrhages, some of which were quite copious. Lilienthal removed the right lower and middle lobes and part of the upper lobe. "Over a year later the patient was in excellent general condition and stated that he was able to dance through seventeen dances without undue effort and without shortness of breath."

<sup>24</sup> Loc. cit.

<sup>25</sup> Loc. cit.

<sup>26</sup> Acute Abscess and Gangrene of the Lung, Boston Med. and Surg. Jour., 171, 49.

<sup>27</sup> Loc. cit.

<sup>28</sup> A Clinic at the Jefferson Medical College, Therap. Gaz., 1921, 45, 474.

<sup>29</sup> Resection of Lung for Posttonsillectomy Abscess, Surg., Gynec. and Obst., November, 1919, 29, 413.

The report of Goldberg and Biesenthal<sup>30</sup> is the most encouraging of all. They detail 3 cases treated by artificial pneumothorax, all of whom recovered. They find that of the 16 cases so treated reported in the literature, 12, or 75 per cent, have made a complete recovery; 2, or 12 per cent, were reported as improved early in the course of treatment; while 2, or 12 per cent, were reported as dead. One of the latter developed a pyopneumothorax following rupture of the abscess; the other having been complicated by pregnancy, epilepsy and asthma.

This is truly a splendid showing, and it has the great advantage that the specially skilled technic required of bronchoscopic or external surgical methods is not required and that the procedure itself is so comparatively free from discomfort and danger.

A larger series of cases is necessary before final conclusions are drawn, but surely no one will quarrel with the conclusion of Goldberg and Biesenthal that "From a comparison of the results obtained in the treatment of acute lung abscess, in addition to the simplicity of the procedure involved, artificial pneumothorax apparently should be the operation of choice."

Treatment of this condition is beyond the sphere of the otolaryngologist, with the exception of the bronchoscopic phase. Lynah's<sup>31</sup> experience in this class of cases has been relatively great, and he concludes that "By the use of the bronchoscope in the treatment of bronchiectasis and pulmonary abscess many patients suffering from these conditions may not only be relieved but even cured by the establishing of proper drainage of the lung. . . . Pulmonary drainage is difficult in cases of circumscribed abscess, but I think the conservative bronchoscopic measures of treatment should be given a thorough trial first before radical major surgery is attempted."

It is possible that by observing certain precautions we can help to minimize the frequency of this condition:

1. We can avoid operating on patients whose throats or general systemic condition causes them to be poor risks.
2. We can set and maintain the highest possible standard of aseptic operative technic.
3. We can adopt whatever position of the patient's head that seems most reasonable to us.
4. We can avoid too deep anesthesia.
5. We can prevent as far as possible the entrance into the bronchi of substances foreign thereto.
6. We can reduce to a minimum the trauma of the throat.
7. We can use surface ties instead of needle-carried ligatures.

<sup>30</sup> The Treatment of Acute Lung Abscess by Artificial Pneumothorax, *Am. Rev. Tuberc.*, 1919, 3, 169.

<sup>31</sup> Bronchoscopic Treatment of Bronchiectasis and Pulmonary Abscess, *New York Med. Jour.*, February 7, 1921, 215.

CLINICAL OBSERVATIONS AND RESEARCH WORK.<sup>1</sup>

BY JOHN B. DEAVER, M.D.,

AND

STANLEY P. REIMANN, M.D.,

PHILADELPHIA.

"As clinical observers we study the experiments which nature makes upon our fellow-creatures. These experiments, however, in striking contrast to those of the laboratory, lack exactness, possessing as they do a variability at once a despair and a delight—the despair of those who look for nothing but fixed laws in an art which is still deep in the sloughs of empiricism; the delight of those who find it an expression of a universal law, transcending, even scorning, the petty accuracy of test-tube and balance, the law that in man, 'the measure of all things,' mutability, variability, mobility are the very marrow of his being."

In these words the immortal Osler, himself the delight and the despair of his admirers, characterizes the basic principles of the relation between clinical observation and research work, the subject we have chosen for these remarks this evening.

Osler makes it plain that medicine is as yet not an exact science but an art. But it is fortunate for mankind that the boundaries of the art have been invaded and its frontiers gradually made narrower by science which not only routes empiricism and gives logical reasons for practices which have stood the test of time, but adds new knowledge with which to carry on with greater certainty the battle for the control and perhaps for the ultimate prevention of disease. To acquire an art, it is needless to say, takes time, takes unceasing enthusiasm and labor, takes experience. The acquisition of a science demands a similar price. In both art and science the first requirement is imagination; without it, we cannot hope to produce either an immortal artist or an immortal scientist.

But imagination without observation, experiment and comparison would lead us no further than merely to the door of progress. It is rare that the artist or the scientist is endowed with all of these qualifications. There are few Pasteurs, few Newtons, few Ehrlichs. Medicine is the most difficult and intricate of all the arts and sciences, and we are confronted at every turn with problems and confusion. If one individual, except he be of the very elect, can hardly master the known facts and put them to use, how then can anyone mind both apply its acquired knowledge and at the same time explore new fields?

<sup>1</sup> Read at the Twenty-fourth Annual Session of the Tri-State Medical Association of the Carolinas and Virginia, Norfolk, Virginia, February 22, 1922.

Fortunately by combining the talents of the two or three or more individuals we are able to muster the best and establish principles with which to labor for the benefit of mankind.

The practical application of this combination of talents, as no doubt you are aware, has its beginnings in the medical school. It is there that the most significant changes have been made, and parenthetically are still required, to lift the study of medicine out of the slough of empiricism in which, to a great extent, it still lingers. The medical school requires on its teaching staff—and to my mind teaching is the essential function of a medical school—the services not only of theorists but more important of practical experienced clinicians, whose observations among their patients prepare their minds and those of their students for the problems living patients suggest. For as Pasteur tersely expresses it, "In the fields of observation chance favors only the prepared mind." One of the significant changes above referred to is the introduction of laboratory methods into the regular curriculum of the medical school. It is in the "do-it-yourself" idea that the student of today has perhaps the greatest advantage over the student of a former time. By gradual steps he advances from the simpler forms of laboratory work to the more complex problems presented by the human laboratory. It is not, however, from the former sources that we should expect to derive the most valuable information. The observations made and the experience gained in this school work should be entirely preparatory.

Without wishing to detract in any way from the invaluable work that has emanated from the various research laboratories throughout the country, carrying on their work independently of a hospital organization, I should like here to record my conviction that the logical place for a laboratory of medical and surgical research is in connection with a well-established, well-conducted modern hospital. "The experiments of nature" can best be observed, studied and applied in a laboratory connected with such an institution. I should therefore like to see more endowments assigned to hospital research laboratories and in turn also I should like to see a more generous attitude on the part of the hospitals in throwing open their doors to students eager to observe, perhaps later to experiment, and finally to compare the results of such observations and experiments.

Every properly conducted hospital contains within itself the clinical material essential for stimulating imagination, observation, etc.; in other words, every patient represents an actual or potential question mark demanding attention.

The real wealth of material necessary for practical research can be obtained only from the hospital. With the study of each patient, whether or not he has been cured, there must accrue a direct benefit to that patient or to his successors. Social betterment is the watchword of our times, and it is a well-recognized

fact that while the care of the sick is the primary and essential function of the hospital, it is not the only one; quite as important is its duty to that supreme question, the improvement of the human race.

The matter of research carried on in conjunction with a hospital has been appreciated for a long time in European centers. Some of the most important and epoch-making discoveries in the conquest of disease, as we all know, have emanated from such institutes. The work of Ehrlich, to cite probably the most trenchant example, was not in a medical training laboratory but in a hospital laboratory. There is little doubt but that to this policy of establishing hospital laboratories, not only of pathology but of bacteriology, physiology, chemistry and all the allied sciences, Germany, for example, owes much of the conspicuous place which she has achieved during the last half-century.

The head of the laboratory should preferably be a pathologist, because pathologic anatomy is still the most important of the fundamental subjects. Furthermore a good pathologist is usually well trained also in bacteriology and physiology, and he is in a position to appreciate investigations into functional activities of the body, normal and abnormal. Most of the questions to be investigated could be such as are of direct clinical value, although it must be recognized that knowledge, provided it is true knowledge, of even the most unpractical and seemingly academic interest only awaits the magic touch of inspiration, perhaps further work, to make it yield abundant fruit. For our purposes animal experimentation, I need scarcely say, is indispensable. And yet in our enlightened country and in other supposedly enlightened countries legislators are kept busy listening to the arguments of individuals who would perforce prevent the use of this beneficial and essential method of investigation.

Our knowledge of most diseases in their progress can be obtained in the most convincing way only by experimental work on animals. In our struggle for the prevention of disease we can use only animals who are susceptible to the disease under investigation, reproduce it in such animals and then endeavor to cure it. One of the main reasons, for example, why we know so little of influenza, which in late years has played such havoc among humankind, is because no one has yet succeeded in transmitting the disease in its human form to an animal, so that it might be accurately studied.

The value of laboratory work to the surgeon is nowadays taken for granted. In diagnosis it has its supreme function in furnishing confirmatory and oftentimes positive evidence; no less valuable are the clinical tests which indicate the state of functional activity, particularly of the kidneys, and which in favor or against operative intervention in certain cases. To the experimental physiologist the surgeon owes his knowledge of how far he can venture in radical surgery—knowledge which he would never have dared to obtain

from the human subject as the experimental object. On the other hand, when a brilliant flash of the imagination, which so often comes in the presence of an emergency, has suggested a new operative procedure, the laboratory investigator immediately begins to study the safety of the method and its rationale. A striking example of such circumstance is the operation of gastrojejunostomy which has become an every-day procedure in most surgical clinics. When confronted with an inoperable carcinoma of the pylorus, Wölfer was about to close the abdomen, when his assistant, Nicoladini, suggested anastomosing the small bowel with the anterior wall of the stomach, thus providing a new exit for the food. Although the operation in its original form proved a poor one from a physiologic standpoint, it formed the basis of study for the development of the methods now in use which have proven of such marked benefit to a large class of sufferers from abdominal disorders. It is difficult to find a more significant example of the value of clinical observations to surgical research than this simple operation. Again, the clinician is often able to apply nature's experiments in a practical way to his surgical work. We need only mention such a phenomenon as a spontaneous cholecystoenterostomy, which is often as successful in relieving distress as the artificial anastomosis which the surgeon, imitating nature, occasionally uses.

These and numerous other instances which might be cited show the importance of well-equipped laboratories as an integral part of a modern hospital. We must emphasize the human as well as the material equipment, for without a well-trained staff of workers in the laboratory, we can make very little progress in our problems. It should be the function of such a research staff to keep abreast of all new suggestions, to offer new methods and to extend knowledge by verification and experiment, and, on the other hand, the wideawake clinician, with problems staring him in the face, should make the best use not only of the hands of this laboratory staff, but of their brains as well. Sir Almoth Wright has said that "Laboratories not attached to hospitals cannot turn out good work without stimulus of fresh material from the hospital—they suffer from paucity of ideas." They, we believe, also lack the mutual inspiration to be derived from the working together of the clinical and the laboratory staff.

The present era is without doubt the era of combined research based on the correlation of clinical observation and experimental inquiry. To it surgery owes its wonderful forward strides since the days of Pasteur and Lister. It is only by the further development of this team work between the hospital and the laboratory that the former can properly perform its function in caring for the sick and the suffering, and the latter can hope to make worthy contributions to the ideal that animates the science and the art of medicine, the prevention and eradication of disease.

## REVIEWS.

---

CLINICAL DIAGNOSIS. By CHARLES E. SIMON, B.A., M.D., Lecturer in Medical Zoölogy, School of Hygiene and Public Health of the Johns Hopkins University. Tenth edition. Pp. 1125; 256 illustrations. Philadelphia and New York: Lea & Febiger, 1922.

THE appearance of the tenth edition of Simon's excellent manual of *Clinical Diagnosis* finds the book materially altered from previous editions. Large sections have been rewritten and the material has been increased by 273 pages over the former edition. Particularly of value to the clinician is the enlargement of the section on blood chemistry. The development of the chemistry of the blood in the last ten years, which is more or less unfamiliar to the average clinician, is given very completely from the clinical standpoint in this new edition. The section on parasitology has been complete rewritten. Numerous other changes have taken place, including the addition of some new plate illustrations. The only adverse criticism that the reviewer might make of the book is in the minute description and direction for the undertaking of so large a number of extremely delicate chemical, biologic and immunologic reactions. It would seem advisable to delete many of them from a book of this character and size. With the large number of new tests that are appearing it might easily be conceived that future editions would become so unwieldy as to lack practical clinical applicability.

M.

OUTLINES OF GENERAL BIOLOGY. By C. W. HARGITT and G. T. HARGITT, Syracuse University. Fourth edition. Pp. 184; 4 illustrations. Philadelphia: Lea & Febiger, 1922.

THE *Outlines of General Biology* is, as a subtitle indicates, a laboratory guide. Notwithstanding a tendency of recent years to develop the laboratory work about a frame of biologic principles, the authors present us with a series of types, on the whole well selected, but with some notable omissions. Although some eighteen animals and five plants are treated, one misses the parasitic worms. In spite of the fact that the book deals with types, the authors



state that it is not a study of types as such, but that its purpose is to illustrate biologic principles. This is true, in a sense, in all type courses.

The order of treatment on the first inspection does not seem logical; but, in reality, as the reviewer knows, it works exceedingly well in actual practice. Beginning with the frog, we are led to cells and from cells to the one-celled organisms. Thence we climb the ladder of life to the fish. However, the authors do not make clear why histology precedes the cell, or why yeast and bacteria are sandwiched in between the fern and the crayfish.

In guiding the students the authors happily combine the method of verification with a series of leading questions—a method in the long run successful; it helps the student over the rough places and urges him to exert himself on the easy roads. Although the book presents no unusual features, it is carefully written and well printed.

C.

---

**X-RAY DOSAGE IN TREATMENT AND RADIOGRAPHY.** By WILLIAM D. WITHERBEE, M.D., Radiotherapist, Presbyterian Hospital, New York; formerly Roentgenologist, Rockefeller Institute; and JOHN REMER, M.D., Radiotherapist, New York Hospital, New York; Consulting Radiotherapist, United Hospital, Port Chester. Pp. 87; 5 illustrations. New York: The Macmillan Company, 1922.

THE dosage set down in the first part of this reference work have been derived from careful experimentation and may be accepted as standard. The part of the book that deals with roentgenotherapy, however, lacks balance. The therapeutics of malignant conditions is covered in four or five brief paragraphs, while one entire chapter is devoted to the treatment of throat infections.

Z.

---

**THE PHYSIOLOGY OF GOUT, RHEUMATISM AND ARTHRITIS.** A Guide to Accurate Diagnosis and Efficient Treatment. By PERCY WILDE, M.D., Physician to the Lansdown Hospital, Bath. New York: William Wood & Company, 1922.

THIS book represents the attempt, based upon extended clinical contact with rheumatic and arthritic patients, to formulate hypotheses as to the nature of these conditions and as to the rationale of some forms of treatment, chiefly those depending on external heat. There can be no gainsaying the wide experience of the author and the best excuse for this book is the clinical viewpoint and correlations which a lifelong interest in the subject has developed. The

author sees the problem fundamentally as chemical and metabolic in nature. By his own definition, however, he is not a chemist and his speculations and experiments in this most difficult of fields are less impressive than are the purely clinical considerations based on his practical experiences.

There are many indications of a careless background, or worse, such as references to the gonococcus bacillus (p. 3) and the bacillus of scarlatina (p. 103). The book may have value to those persons interested in arthritis who are willing to read through considerable untrained speculation for the sake of such "leads" or suggestive visual angles as are afforded.

P.

THE PRACTICE OF MEDICINE IN THE TROPICS. VOLUME II. Edited by W. BYAM, O.B.E., Lieut.-Col., R.A.M.C. (retired), Lecturer on Tropical Medicine at St. George's Hospital Medical School; and R. G. ARCHIBALD, D.S.O., Major, R.A.M.C. (retired), Director of the Wellcome Tropical Research Laboratories, Sudan Government, Gordon College, Khartoum. Pp. 835; 245 illustrations. London: Henry Frowde, Hodder & Stoughton, 1922.

THE second volume of this admirable work more than fulfils the promises held out in the first volume. In this second volume the editors have taken up bacterial disorders, spirochetal and protozoal diseases. The character of the work and the type of material presented may be judged by the mention of the names of some of the authors: Castellani, Heiser, Sir Leonard Rogers, Manson, Ashford, to mention just a few of those who are well-known authorities on a particular branch of tropical disease who have written sections of the book. The third volume has not yet appeared. Undoubtedly it will maintain the standards set by the two previous volumes.

M.

QUESTIONS NEUROLOGIQUES D'ACTUALITÉ. Pp. 552. Paris: Masson et Cie., 1922.

THIS octavo volume contains a series of twenty lectures, given during June and July of 1921 in the "Grand Amphithéâtre" of the Paris Faculty of Medicine, by the most prominent chiefs of the neurologic services of the various Paris hospitals, plus one by Dr. S. A. K. Wilson, of London. Each man chose the subject in which he was most interested at the time and gave the latter-day views thereon—a sort of "dernier mot." Dr. Kinnear Wilson starts off with a discussion on the pathogenesis, diagnosis and

pathologic physiology of progressive lenticular degeneration. From a clinical standpoint he brings out the fact that possibly the duration of the disease may be up to ten years or somewhat more than an intention tremor, with the objective characteristics of the tremor of paralysis agitans as the most frequent type of involuntary movement, while the choreo-athetoid movements are rare. This is simply the *résumé* of a portion of his talk and there is a great deal of "meat" in it, as well as in every one of the other lectures given by French neurologists.

The specialist in neuropsychiatry can hardly do without this book if he intends to keep abreast of the times in his own chosen subject. O.

---

THE SCIENCE OF OURSELVES (A SEQUEL TO THE "DESCENT OF MAN"). By SIR BAMPFYLDE FULLER, K.C.S.I., C.I.E. Pp. 326. London: Henry Frowde, Oxford University Press, Hodder & Stoughton, Warwick Square. E. C., 1921.

THE aim of the book is to "set out an inferential theory which will explain the origin and course of feeling, thought and behavior." In the "Epilogue" the author states that the views to which his inquiries have led him are "disillusioning." Through history one reads "a miserable tale of pain and suffering." If we boast of our economic civilization, all we need to do to take the wind out of our sails is to walk through the slums of any commercial town to be impressed with "such degradation as is hardly to be found amongst the poorest classes of the East." About the same is to be said of our private lives, in the opinion of the author. His remedy apparently is the necessity of our realizing that anger, pride and jealousy are "merely nervous reactions and can be resisted."

After a fairly careful reading of the book, the reviewer is forced to admit that he does not clearly see just how the author demonstrates the methods of such resistance. In brief, the reviewer is impressed by two features of the book: One a matter of content, pessimism hinted at if not frankly expressed; the other a matter of style, a style that is not wholly lacking in clearness, but is at least heavy and at times cumbersome.

The latter is probably due to the fact that much of the book, at least three-fourths of it, deals with or in matters that, while they profess to be the conclusions of recent research, smack much of the old school of descriptive psychology.

The opening chapters promise more than is actually fulfilled, and, but for a few variations in a few keys, are hardly more than has already been expressed by Cannon or Crile, and in addition seem to be a sort of potpourri of the ideas set forth by these men and Freud. In brief, one does not lay down the book with a feeling

that he has such clear-cut impressions as he would like, independently of the question as to whether he has read something which he would accept or not.

Part I deals with "Nervous Activities" and Part II with "Motives and Behavior." There are, without question, paragraphs in Part I that are stimulating and helpful. There is much to be said for the author's conclusion concerning autosuggestion "in which one physical or nervous condition produces another with which it has been associated in rhythm," kindly acts being associated in experience with kindly feelings, smiles with pleasure, etc., and that if we "act in kindly fashion, although with no sympathetic motive, a glow of kindly feeling may follow." Even here, however, we are dangerously close to the James-Lange theory of emotions, which Dana has recently refuted in certain experimental studies.<sup>1</sup> But granted that we are willing to accept the author's conclusion that kindly acts are associated with kindly feelings, etc., it is difficult to follow him in the intricacies of such conclusions as he reaches in his tabulated note on "The Appetites, Emotions and Will," in four columns such as:

Nervous planes contributing.	Emotion.	Stimuli.	
The physical reinforced by the psychic and the mental (memory)	Fear	{ The strange, dangerous or antagonistic in things or in persons }	{ The strange would not be appreciated unless the familiar was established by nervous association (memory). }
	Sexual love	{ Sexual cravings centered upon one of the opposite sex }	{ Arise as instinctive impulses, but are spiritualized by psychic and directed by mental influences. }
	Maternal love	{ Maternal cravings centered upon a child }	

Why it is difficult to follow him may be made a little clearer by merely enumerating his column of emotions in full, which include: fear, sexual love, maternal love, the love of "attachment;" faith, respect and pity, loving kindness, sympathy and their contraries; anger, hate, revenge, jealousy and scorn, curiosity, courage, emulation, industry, morality; assertive volition, tentative volition and selective volition.

When we get through this maze we feel a little as though we were turning back the wheel to the time of medieval speculative philosophy and wonder to what end modern psychiatry may go if it allows itself to wander in such pastures.

It may be maintained that this review is beside the point in assum-

<sup>1</sup> The Anatomic Seat of the Emotions: A Discussion of the James-Lange Theory, Arch. Neurol. and Psychiat., December, 1921, pp. 634-639.

ing that the author is treating of things medical, but one can hardly avoid assuming such from the nature of the titles of Part I on "Nervous Activities." Under "Motives and Behavior" the reviewer feels himself still more in a maze. He does fairly well as he attempts to follow what the author says on Fear, Courage and Anger; but when he tries to follow him on "Respect," "Faith," "Obedience," "Emulation," "Industry," "Morality," "Expectative and Explorative Behavior," "Appreciative and Imaginative Behavior," etc., he feels himself a little out of his element and frankly admits that he is on surer ground when he follows the work of such countrymen of the author as Rivers in his book on "Instincts and the Unconscious."<sup>1</sup>

It is not the reviewer's purpose to overlook deliberately certain values of such works as that under consideration. They have a place. The book in question deserves credit for even having attempted to make "a case for bringing the mainsprings of our behavior under the light," as our author puts it in the last sentence of his epilogue.

W.

<sup>1</sup> *Instincts and the Unconscious: A Contribution to the Biologic Theory of the Psycho-Neurosis*, Cambridge University Press, 1920.

# PROGRESS OF MEDICAL SCIENCE

---

## MEDICINE

---

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF  
CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

---

**Arterial Myohypertrophy.**—BILLARD and MOUGEOT (*Presse méd.*, 1922, No. 61, p. 655) state that one of the functions of muscular arteries is the absorption of shocks from the movement of the mass of blood in the course of muscular work. Thus, those who do heavy manual labor are apt to have thickened peripheral arteries, which are the results of physiologic rather than pathologic changes. This induration is to be distinguished from atheroma by its smoothness, and from sclerosis by the absence of tortuosity.

**The Mechanism of Compensation.**—STARLING (*Presse méd.*, 1922, No. 60, p. 643) emphasizes the "law of the heart," which postulates that the energy with which fibers of cardiac muscle contract is a function of their length, and, therefore, of the state of dilatation of the heart. Basing his conclusions upon carefully controlled experiments with the heart-lung preparation, he shows that fatigue of the heart reveals itself first not in failure to accomplish the work demanded of it, but in the impossibility of accomplishing this work without undergoing a considerable dilatation. Compensation implies always an increase in the work of the heart; the demand for increased work may be met by increased rate of beating or by increased output per beat. The central fact of failure of compensation is a diminishing of the cardiac output below the amount demanded by the exigencies of the individual case. The classic symptoms of congestive failure are the direct results of this reduction in output. Therapeutic measures are of value as they increase the output or decrease the demand. The

blood-pressure in failing compensation is not low, and in cyanotic cases may be elevated; the importance of this from the viewpoint of the coronary circulation is obvious. The degree of possible dilatation, and hence the amount of reserve, is limited by the pericardium, and may be limited by an inextensibility of the myocardium resulting from a fibrous infiltration of its tissues.

**Angina Pectoris.**—LEVINE (*Jour. Am. Med. Assn.*, 1922, 79, 928) reports some interesting points that developed in the study of 103 cases of angina pectoris at the Peter Bent Brigham Hospital and in his private practice. His conclusions are as follows: "The disease is much more common in males than in females, while vascular hypertension, which plays an important role in the etiology of the disease, is, on the contrary, more common in women. Physical work may account for this discrepancy. The typical patient with angina is a strong muscular and well-set person. The disease seems to be comparatively rare in the underdeveloped, poorly nourished and weak. In this series syphilis was an etiologic factor in only 6 patients. There were 7 who had diabetes mellitus, and 5 who had gout. Organic valvular disease was rarely found associated with angina pectoris. Two patients had typical mitral stenosis, and there were 2 young patients with rheumatic disease of the aortic valves. The average systolic blood-pressure was 160.6 mm., and the diastolic was 95 mm. About two-thirds were between 140 and 200 mm. Observations on the blood-pressure in a few cases were made in relation to the onset of the attack of angina and the administration of nitroglycerine. Two patients showed a marked increase with the onset of the attack, and then a fall as the attack subsided after the nitroglycerine had been given. In a third the change was not significant, either as the attack developed or as it subsided under treatment. Examination of the heart in many cases was negative. Of these 103 patients, 47 showed no murmurs, 49 had a systolic murmur at the apex or base, and 7 had a diastolic murmur. The heart was generally found hypertrophied on ordinary examination or by orthodiagraphy or electrocardiography. An occasional patient showed no hypertrophy even after the most careful search. The dominant rhythm of the heart in angina pectoris was regular, although there were occasional extrasystoles. Only 1 out of 103 showed persistent auricular fibrillation. This is particularly striking, because during the same period of time persistent auricular fibrillation was observed in about 200 other patients suffering from chronic myocarditis, who, in general, were of the same age as those with angina. There therefore seems to be a distinct incompatibility between angina pectoris and auricular fibrillation. Patients with auricular fibrillation are not likely to have or to develop angina pectoris, and, *vice versa*, those suffering from angina pectoris do not develop auricular fibrillation. The quantity and loudness of the heart sounds are of practical importance in angina pectoris, especially the first heart sound at the apex. The diminution of the intensity of the apical first sound may be of aid in diagnosis and prognosis. Edema of the limbs and swelling of the liver are rare, but congestive rales at the bases of the lungs are common, especially in those patients with cardiac infarction. The electrocardiograms were

occasionally normal in appearance, and frequency showed only slight alterations. It is important to distinguish attacks of cardiac infarction from those of ordinary angina pectoris, for where the prognosis of the former is generally only days, that of the latter may be years. The patient having cardiac infarction shows the picture of shock and is cyanosed; the pain may last many days, and is not relieved by nitrites, or even at times by morphine; the pulse is likely to be a little rapid and small; the systolic pressure falls sometimes as low as 90 or 80 mm.; rales develop at the bases of the lungs, and the liver may become engorged and tender. A leukocytosis of 20,000 or more frequently develops. Occasionally the violent pain is localized in the upper abdomen, and there may be nausea, vomiting and marked rigidity of the muscles in the epigastrium. There are, therefore, some patients with cardiac infarction who present the typical picture of an acute surgical abdominal condition."

**Urea Kidney Test.**—ADDIS (*Arch. Int. Med.*, 1922, 30, 378) attempts to draw quantitative structural deductions from functional results. In this, the first paper of a series, he discusses the "urea-ratio test." Two essential conditions are required. One is that the kidney should be placed under circumstances which call for great activity in urea excretion. The other is that there should be an absence of certain specific renal stimulants and depressants. The first is met by the administration of an amount of urea which will raise the concentration of urea in the blood reaching the kidney, while at the same time a diuresis is induced by water-drinking. The second is fulfilled if the test is carried out in the morning, before the subject has taken food, and if the collections of urine and blood are not commenced until three hours after the urea has been taken. The details of the procedure used in clinical work are as follows: At 6 A.M. the patient slowly drinks about 1000 cc of water, in which urea is dissolved. When the blood-urea concentration is between 15 and 25 mg. per 100 cc 30 cc of urea are given. If the blood concentration is already as high as 60 mg. of urea per 100 cc no urea need be taken. At intermediate blood-urea levels appropriate quantities of urea are administered, so that when the first blood is collected it should have a concentration of between 60 and 90 mg. of urea per 100 cc. At 7 A.M., and every hour thereafter until 11 A.M. the patient drinks two glasses of water. No breakfast is given. Urine is voided every hour, but at 9 A.M. (the time at which urination is completed is noted to within thirty seconds) and at 10 A.M., 11 A.M. and 12 noon urine is passed directly into special bottles and the exact time noted. Blood is obtained at the middle of each of the three-hourly periods, over which urine is collected. The urea content of these urine and blood specimens must be estimated with a high degree of accuracy, for even small errors may markedly influence the ratio if they happen to be in opposite directions for the blood and for the urine. From the formula

$$\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc of blood}}$$



can be measured the amount of secreting tissue in the kidney. The author promises that examples of the application of this method in clinical work will be published in a later paper. He has found this method of value in the diagnosis, prognosis and treatment of Bright's disease.

---

**Oxygen Therapy.**—BARACH (*Jour. Am. Med. Assn.*, 1922, 79, 693) discusses the recent advances in the therapeutic application of oxygen. He points out that anoxemia may have serious consequences, particularly if of considerable duration; that it occurs frequently in clinical conditions; and that it may in many instances be prevented or relieved by proper oxygen therapy. The indication *par excellence* for the administration of oxygen is acute anoxemia, such as may occur in pneumonia, cardiac failure, severe hemorrhage, pulmonary edema, carbon-monoxide poisoning, high altitudes, nitrous-oxide anesthesia and so on. Improvement after oxygen therapy may be manifested by changes in the degree of cyanosis, the pulse-rate and the mental condition. Oxygen therapy should be used as much to avoid the dangers of anoxemia as to relieve symptoms. Various methods for the administration of oxygen are described. It is pointed out that the method used should deliver a mixture containing 40 to 60 per cent of oxygen.

---

**The Heart in Hypertension.**—LUTEMBACHER (*Bull. méd.*, 1922, 31, 616), in a contribution, which is one of a series of papers by prominent French writers in a symposium upon hypertensive cardiovascular disease, reports clinical and electrocardiographic evidences of the effect of hypertension upon the heart. He traces roughly the reaction of the heart through the following successive states: Concentric hypertrophy, sudden or gradual, failure of the left heart, tachycardia, dyspnea, palpitation, slight precordial pain, frequent premature systoles, cardiac decompensation and frequently angina. He points out the clinical importance of the fact that slight precordial pain is often an initial evidence of myocardial failure and may be a precursor of angina. Tracings of ventricular premature systoles are shown, and the author has found that such premature contractions arise within the ventricular musculature are more significant of myocardial disease than are those which arise within the course of the His bundle. Inversion of the T wave and low R waves are noted. A sharp clinical distinction is made between the precordial pain incident to hypertension and myocardial failure, on the one hand, and true angina, on the other. He speaks of the pain of heart failure as "decubitus angina" as contrasted with true angina—the "angina of effort." Either type, however, may be fatal, and the essential differences lie: (1) In their mode of production; and (2) in the fact that the decubitus angina is associated with cardiac dilatation and resists the usual methods of treatment that are employed for the prompt relief of true angina (the angina of effort). The paper ends with a discussion of thrombus formation in hearts subjected to the strain of hypertension.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**An Analysis of a Series of Case Records Relative to Certain Phases of Breast Feeding.**—DIETRICH (*Jour. Am. Med. Assn.*, 1922, 79, 268) bases his analytic study on the records of 1000 records of cases from his private practice. Of 371 cases weaned during the first three months the reason for weaning was ascertained in 337 instances. A total of 95 of these were weaned because of insufficient milk or insufficient gain. These two reasons were recorded in more than 20 infants before the end of one week of life. The great majority of these 95 infants, with proper care and, if necessary, with complementary feedings, could have been partially or entirely breast-fed. Curds in the stool, convulsions, pertussis, menstruation of the mother, cleft palate, spastic paralysis, prematurity, acid and salty milk, failure of the mother to nurse previous children were given as reasons that were given for weaning. The author thinks that the subject should become the point of discussion in medical societies and journals so that the physicians may become more cognizant of the dangers of weaning and better informed as to the indications for taking away breast feedings.

**Infantile Eczema.**—SPOHN (*Can. Med. Assn. Jour.*, 1922, 12, 461) reports thirty-three breast-fed infants, twenty-two infants fed on cow's milk and sugar, and fifteen with mixed feedings and cow's milk. In 39 per cent there was a definite family history of either eczema, persistent head colds, bronchitis, and asthma. Fifty-seven per cent were overweight or normal in weight. In 70 per cent of the breast-fed babies of this series there was a history of being fed every three hours or oftener. In 63 per cent there was a definite history of fat intolerance. In 56 per cent sugar had an irritating effect on the skin condition. Dietetic management and local treatment usually met with prompt response. Sixty-five per cent were clear of eczema in less than three months, and remained clear as long as treatment was followed. Twenty-four per cent became clear of the eczema in from three to nine months. Three cases only showed slight improvement.

**Alkalies in Acidosis.**—CLARKE and DOW (*Arch. Pediat.*, 1922, 34, 449) undertook a series of experiments to determine the proper dosage of certain alkalies, the best alkali to be administered and the ability of the infants to absorb the alkali. They found that, in administering soda bicarbonate by mouth, absorption was very slow, and probably too much delayed to do much good in acute cases of acidosis. Ringer's solution, when administered by the intraperitoneal route, had no appreciable effect in raising the carbon-dioxide-combining power of the blood. A 4 per cent solution of soda bicarbonate, administered

by the peritoneal route, is almost negligible in its effect, insofar as increasing the carbon-dioxide-combining power of the blood is concerned. Their observations led them to feel that larger doses than a 4 per cent solution of soda bicarbonate administered intraperitoneally would have a very distinct influence in raising the blood alkalinity, but there is then the danger of an alkalosis. Solutions of soda bicarbonate given by rectum are absorbed, but probably more slowly than by mouth. The Van Slyke apparatus is an aid in diagnosis and also in making differential diagnosis. In common with other observers, the authors believe that the alkalies, when given in the usual ways, have very little if any curative effects, and they think that the work on this problem so far has only been preliminary to what will be developed.

---

**A Critical Study of 61 Cases of Asthma and Eczema in Infancy and Childhood Controlled by Cutaneous Protein Sensitization Tests.**—HERMAN (*Am. Jour. Dis. Child.*, 1922, 24, 221) studied 31 cases of bronchial asthma in children from one to fourteen years of age, and 30 cases of eczema in children from five weeks to seven years of age. A total of 4520 tests were performed, 979 of these being tests with the same proteins repeated. An average per patient of 96 different proteins were tried on the asthmatic group, and 22 different proteins were tried on the eczema group. There was a much greater incidence of protein sensitization in children with asthma and eczema than in normal children. Approximately  $\frac{1}{2}$  in every 28 or 29 tests performed gave a positive reaction, and 1 in every 11 or 12 tests was either positive or doubtful. As many as 14 of the asthma cases and 13 of the eczema cases gave no indication of hypersensitivity as determined by skin tests. The proteins of egg, rabbit, hair, cows' milk, mustard, chicken feathers and goose feathers, lamb, chicken, goose and duck, gave the most frequent positive reactions. The goose and duck, gave the most frequent positive reactions. The writer classifies cases into sensitive and non-sensitive, and further groups then according to the type of proteins to which they were sensitive, such as food, animal, epidermal, pollen or bacterial. None were found that were sensitive to bacterial proteins. He stresses the importance of focal infections as an etiologic factor in these children. Sensitization to the proteins of rabbit hair, which is commonly found in many homes, is a frequent occurrence. A striking point noted was the multiplicity of causes which necessitates the intensive study of every case.

---

**An Analysis of the Cause of Fever in Early Life.**—GITTINGS and DONNELLY (*Pennsylvania Med. Jour.*, 1922, 25, 842) point out that the significance of a short illness in a child is often missed, chiefly because febrile disturbances are so common that they are apt to be overlooked or inconsiderately studied. As an example, may be cited a short attack of croupous pneumonia or a mild scarlet fever being entirely misjudged until an empyema or a nephritis is present. The important initial symptoms are often overlooked by the mother, and the case described as of sudden onset. Especially is this true of tuberculosis, and a history of a few days' illness on careful questioning

may be found to really be an illness of weeks. One of the great advantages of the pediatric practice is the feasibility of making complete physical examination. There seems to be no excuse to fail to elicit ordinarily obvious findings, and this will rarely occur if the child is stripped and the examination is thorough. In all cases of tonsillitis it is urged that the entire body be examined to preclude overlooking scarlet fever. Careful examination should be made of the lungs of every patient. Rarely will the pneumonias be missed under these circumstances. In all cases examination of the ear drums is urged. In cases failing to reveal the cause of the fever by other means the urine should be examined to determine the possibility of pyelitis. A general examination of the urine and a leukocyte count whenever feasible is recommended, to obviate the danger of failing to diagnose a serious condition of few outward manifestations.

---

**Some Diagnostic Points in Scarlet Fever.**—MIXSELL (*New York Med. Jour.*, 1922, 114, 159) made an analysis of 1500 cases of this disease. He observed, in addition to the usually recognized symptoms, special symptoms that are seen, but not, as a rule, recognized. In the præruptive stages there is seen a thickening of the mucous membrane of the cheeks and gums associated with reddening. The dorsum of the tongue is dark red in color and barely coated. The paratonsillar lymph nodes at the angle of the jaw are enlarged and tender to the touch. The mucosa of the soft palate and pharynx is greatly reddened, the redness being sharply bounded at the hard palate. The uvula may be red and edematous. In the eruptive stage there are fine puncta on the tonsils and palate, and the lips are much redder than usual. The rash appears on the temples. The cheeks are extremely red, the discoloration being confluent and spreading over the bridge of the nose. The tip of the nose, the upper lip and the chin are pale, presenting a triangular section of skin with the base downward. This is called the circumoral, or perioral pallor, and is a very important diagnostic point. There is marked involvement of the flexor surfaces of the joints of the extremities, especially of the antecubital and popliteal spaces. There may be grooving, ecchymotic spots or small petechial hemorrhages, or a distinct blotching. With the exception of the joint surfaces of the upper extremity, there is little involvement from the upper arm to the lower part of the forearm. An examination of the palms and soles with a magnifying glass shows no puncta, but does show a distinct erythematous blush. The rash of scarlet fever is always generalized and never confined to one part of the body. Pressure of the fingers on the skin will obliterate the rash. In some cases pressure on the skin of the abdomen will produce an anemia, greenish or icteric in color. Scratching of the skin with the finger-nail will cause a red line with an area of distinct pallor (*raies blanches*) on either side. This is not seen in all cases. The tache cerebrale differs from this in that it has no area of pallor on either side. The *raies blanches* are of aid in diagnosis as evidence, not as proof, as similar skin reaction often follows diphtheria antitoxin or other sera. Scarlet fever is often very difficult to diagnose in negroes. A point to be remembered is that strong pressure on the skin, especially on the soft parts of the upper arm or abdomen, will

sometimes reveal the typical scarlet rash in the pallor which results. The skin is without the shininess seen in health and is more intensely black. In the post eruptive stage purpura is sometimes seen, and is probably caused by sepsis. Slight pressure sometimes will cause numerous petechial hemorrhages. This is due to the fact that the bloodvessel walls have become more friable. In the stage of desquamation pinholing is seen. Large flakes of desquamation with a perforated center determines this diagnostic point. The bursting of an inflamed skin papilla causes a small breach in the skin, which is at first small, but which increases in size, and soon becomes visible as a pinhole in the cuticle. This is best seen on the neck and chest and on the outer surfaces of the upper extremities. Peeling from the hands, feet, fingers and toes sometimes result in the epidermis coming off entirely in a cast. Finger desquamation is pathognomonic of scarlet fever. There is also a thickened parchment-like feel of the balls of the fingers, followed by a white line at the juncture of the pulp of the fingers with the nails. Scaling of the nails or cracking, especially of the thumbs, occur from the sixth to the eighth week. At the beginning of this stage the tongue is dry, red and glistening after the lingual mucosa begins to exfoliate. This is called the beefy tongue, and is the earliest evidence of desquamation and may start on the fourth day of the disease. Where there is only a little desquamation of the heels the anterior surfaces of the fingers and toes usually show desquamation. This, and the development of late nephritis, may prove a diagnosis where the rash and other signs have been atypical.

---

**The Basal Metabolism of Prematurity.**—TALBOT, SISSON, MORIARTY and DALRYMPLE (*Am. Jour. Dis. Child.*, 1922, 24, 95) present this report of 7 of the 12 premature infants that they have studied, showing the relation of the caloric intake and the weight curves. They were unable to find anything in the literature where this comparison was made, although there is much data as to the caloric intake and requirements of premature infants. These infants had high pulse-rates, unstable temperatures, and were at first too weak to nurse on the breast. They were either fed by a Breck feeder or a tube. Breast milk was given wherever possible, but it was often necessary to supplement dilute cow's milk formulas. It was interesting to note that the greater the difference between the basal requirements and the caloric intake, the greater the weekly gain in weight. There was also a tendency for the caloric intake to reach close to two and a half times the basal findings before a satisfactory gain in weight was noted. A continuous gain in weight did not, as a rule, result until the babies received a total of from 150 to 200 calories in the food. Satisfactory gains in weight did not result in this series of cases until the babies were able to digest approximately 200 calories in the day. The caloric intake per kilogram of body weight was high in all cases. This is in keeping with the findings of previous investigators. The basal metabolism determinations were strikingly low no matter how they were charted. This low metabolism seemed to be dependent upon the fact that there is a very small amount of active heat-forming tissues in these incompletely developed infants. This evidence is

contrary to the generally accepted belief that the heat value of the metabolism is proportional to the body-surface area. Premature infants apparently produce only so much heat as is necessary for their well-being in the most advantageous surroundings. It is a well-known fact that the deprivation of external warmth from premature infants results in a subnormal temperature. They think that this is an evidence that the active heat-forming protoplasmic tissues are unable to respond to the excessive heat loss from the body, and, as a result, there is a subnormal temperature, and that the amount of heat formed depends upon the amount and tone of the active protoplasmic tissues, and not, primarily, on the size of the surface of the body of these infants. Close observation of premature infants shows very little muscular activity, and they were unable to obtain any data which would lead them to suppose that the heat used up in exercise in premature infants during the day was more than 10 per cent over the basal metabolism. The loss of calories in the excreta of infants is usually less than 10 per cent of the food intake, unless there are four or five large curdy stools a day, in which case the loss may be as high as 20 per cent. There is left, therefore, a proportionately large number of calories for growth.

**Influenzal Meningitis.**—RIVERS (*Am. Jour. Dis. Child.*, 1922, 24, 102) reviews the literature of this disease representing 197 reported cases. He also reports 23 new cases. He found that influenzal meningitis was a disease of infancy, 79 per cent of the cases occurring in patients under two years of age. The mortality in 220 cases was 92 per cent. Of the 17 cases that recovered, 12 were two years or older. There is no typical clinical picture of influenzal meningitis, and many cases are probably overlooked. There is usually a polymorphonuclear leukocytosis. From the case records it is possible to say that the meningitis might have been primary in the majority of instances. Influenzal meningitis is probably a carrier-borne disease. The seasonal and yearly incidence of influenzal meningitis and of epidemic influenza and pneumonia do not coincide. The meningitic strains of influenza bacilli are closely allied to each other and differ from the ordinary respiratory strains of *Bacillus influenzae*, particularly in their serologic reactions and in their pathogenicity for rabbits.

## OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

**The Importance of Amniotic Liquid in the Preservation of Fetal Life.**  
—KRANULA (*Monatschr., f., Geburtsh., u., Gynäk.*, 1921, 55, 199) has studied the relation existing between an abnormal condition

in the amniotic liquid and the condition of the child. Where this is in excess, although children may be born living, they die soon after birth, but 3.78 per cent of them survive their birth for a time and but 1.03 per cent of these children are normal. There seems to be no difference, so far as the chances of the child are concerned, whether there is but one child or whether there are two in the uterus. Where twins are present, the children are more often normal than where but one child is born. While twins may be born apparently normal, their ultimate chance of life and their power of resistance is no better than those of the one child. Where the amniotic liquid increases very rapidly during pregnancy, one must not expect that the infant will survive its birth. In view of the unfavorable prognosis for children the treatment of this condition by puncturing the uterus through the abdominal wall should be abandoned. This procedure is useless and in many cases is not without considerable danger. The one method of treatment which promises good results is to puncture the membranes through the cervix.

---

**The After-history of Children Born by Cesarean Section.**—DENCKER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1921, 55, 207) is not content to take the results as ordinarily reported of children born by Cesarean section. It seems to him important to ascertain whether the operation really improves the child's chance for life or whether it increases its mortality or morbidity. He finds that children born by Cesarean section, as they develop, are in no way placed at a disadvantage with those children born spontaneously. It is true that in Cesarean section a child frequently comes into the world apneic; it is also true that children are often born after various sorts of birth in asphyxia. If in both these conditions a child is brought to breath naturally, they develop quickly and well, and neither condition has a permanently bad result. The narcosis of the mother does not seem to injure the child. The death-rate of children in the first month of life born by Cesarean section is estimated at 4.6 per cent, while the mortality of children in the first month of life born in other ways is 6 per cent. One cannot trace any increase in the mortality of children born by Cesarean section to the operation itself. Of those children born living by Cesarean section 95.4 per cent left the hospital in good condition. The physiological loss of weight in children born by Cesarean section is less than that of other children. Cesarean children, however, take a longer time to regain their initial weight, this lasting from twenty-one to thirty days. The further mortality of Cesarean children is found by studying mortality rate during the first three years of life, when it is found that 81.5 per cent of Cesarean children live through the first year, contrasted with 73.5 per cent of children born of married parents by natural birth, and 51.5 per cent of children born of unmarried mothers but in normal labor. The death-rate of children born by Cesarean section to married mothers is less, because under these circumstances the child usually has better care. The Cesarean child develops well physically and mentally, only 7.3 per cent are not well developed. In all the cases studied there was delay in nervous development in but one, and this child could not be called an idiot. Paralysis, epilepsy, chorea, spasms and other forms of nervous diseases were not seen in these children. One child had convulsions, which resembled somewhat mild epilepsy.

The minor nervous affections of children such as enuresis, night terrors, tetany and headache were no more common in Cesarean than in any other children. If all of the factors be taken into consideration it will be found that children born by Cesarean section are in no way injured physically or mentally. On the contrary they are better developed, often larger and better nourished than other children. In deciding upon the operation the obstetrician may conclude that he is giving the child a better chance for life and health than if it were to be born in any other way.

**The Influence of Pituitary Extracts in Exciting Labor Pains in Pregnancy.** — HELLMUTH (*Zentralbl. f. Gynäk.*, Nr. 37, September, 1921) has used this substance during the first stage of labor in 10 cases, in 8 of which it seemed to produce a decided effect, but in 2 of which it failed. During the second stage of labor he employed it in 34 cases with a successful result, and in 1 case without result. In all it was given 45 times, in 30 followed by an immediate effect. Among the 30 cases where prompt result followed were 8 in whom the so-called analgesia or twilight sleep had been employed. The drugs given to annul pain seemed to prevent the efficient uterine contraction and to make necessary the use of this remedy. It was used in 8 patients to check postpartum bleeding with success. The writer describes the case of a multipara whose labor was delayed by weak uterine contractions, for which this substance was administered. The child was 52 cm. long, weighing 3100 grams. The child was born in normal position and presentation, asphyxiated, with strong but greatly retarded heart beat; there was no effort at respiration. The heart continued to beat for thirty minutes, after which the child died. Efforts at resuscitation were fruitless. At autopsy, atelectasis of the lungs was found, with fatty degeneration of the heart muscle. There was no injury to the brain and no evidence that the membranes or bloodvessels had been injured. Some who have reported similar cases would say that an overdose had been given, and that the remedy had passed through the placenta into the body of the child, while others might think that some essential lesion in the heart was the cause of the death. In order to test the remedy further, it was tried in 4 other cases, but it was given in vain in 3; the uterus reacted very rapidly even during the time of the injection. The writer has also tried this remedy in 5 cases of abortion, where it seemed to control hemorrhage and promote involution in the puerperal periods. During the puerperal period the lochia was normal and no distinct effect of this substance could be detected. The writer has also used it to relieve the retention of urine in puerperal cases and in paralysis of the bowel after surgical operations.

**Pregnancy After Nephrectomy.**—In the *Journal of the American Medical Association*, November 19, 1921, MATTHEWS publishes an interesting paper upon this subject. His personal experience numbers four cases of women who had had nephrectomy and who subsequently gave birth to children. The first of his cases had the kidney removed for tuberculosis and made a good recovery after the operation. Pulmonary tuberculosis did not develop and the patient had a successful pregnancy and labor. The second case was also one of tuberculosis



in which a kidney had been removed. She subsequently developed albuminuria and the remaining kidney evidently became badly damaged. His third patient had the right kidney removed for suppurative nephritis. She subsequently had pyelitis in the remaining kidney during pregnancy, and had a premature labor, from which mother and child recovered. The fourth case had tuberculosis of the left kidney and ureter, upon which the operation was performed. She recovered from the operation, and subsequently had a spontaneous labor with breech presentation, mother and child making a good recovery. In all, the writer has quoted the histories of 265 labors, occurring in 241 women in whom a kidney had been removed. Of these labors 250 were normal and 15 complicated, with two deaths. The writer believes that after nephrectomy, pregnancy follows its normal course. It is but little more dangerous for mother and child than pregnancy under normal conditions, provided the remaining kidney is performing its functions properly. A slight albuminuria of moderate degree occurs in a certain proportion of the cases of pregnancy after nephrectomy, during the last four or six weeks, which under appropriate treatment usually clears up. In the thirty-seven collected and four personal cases herewith reported, 60 per cent showed albuminuria during the latter weeks of pregnancy. When nephrectomy has been performed for unilateral renal tuberculosis, it is imperative that the patient be free from symptoms of tuberculosis in the bladder, ureter, remaining kidney and lungs or elsewhere for three years or more before pregnancy is allowed to supervene. Pregnancy after nephrectomy for malignant tumors of the kidney should not be allowed under any circumstances. Pregnancy after nephrectomy should be terminated immediately on the advent of frank renal insufficiency, as shown by the relation of the nitrogenous products in the blood and urine. The likelihood of a severe "pregnancy pyelitis" or pyelonephrosis in the remaining ureter or kidney must be kept in mind, particularly if the remaining kidney be the right, and on the appearance of either condition immediate termination of the pregnancy is demanded. Labor in pregnancy after nephrectomy takes place without complications referable to the remaining kidney. The reviewer has had occasion to observe a patient whose kidney had been removed for tuberculosis and subsequently became pregnant. During the latter weeks of pregnancy, the urine showed evidence of kidney insufficiency; but very simple treatment in hospital was sufficient to carry the patient safely through her pregnancy and labor. After the birth of the child the urine became normal. Lactation is not interfered with and therefore, except for special reasons, nursing should be carried on in the usual manner. Marriage is permissible in nephrectomized women, provided the remaining kidney has functioned in a normal manner for one year or more. If the nephrectomy was for unilateral renal tuberculosis and a complete cure has been accomplished, as shown by the absence of symptoms in the remaining kidney or elsewhere for three years or more, marriage is still permissible. Finally, there is urgent need for more scientific and systematic study of the nephrectomized woman, both in the nonpregnant as well as in the pregnant state. A well "worked-up" report, including all laboratory methods for the determination of kidney function and urinary excretion, should be published of every case of pregnancy after nephrectomy.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

**Bismuth Salts in Syphilotherapy.**—The use of bismuth salts in the treatment of syphilis has recently occupied the attention of a number of French authors. Among the earliest contributions on the subject were those of SAZERAC and LEVADITI (*Ann. de l'Inst. Pasteur*, 1922, 36, 1) and FOURNIER and GUÉNOT (*Ibid.*, p. 14). The first-named authors credit Sauton and Robert with the original conception of using this metal in the form of sodium-potassium tartrobismuthate in the treatment of the spirochetosis of fowls. Sazerac and Levaditi experimented with a number of bismuth salts in the form of local applications, mouth and rectal administration, subcutaneous and intramuscular injections. A limited amount of experimental work on infected rabbits apparently demonstrated the capacity of the drug to cause the involution of lesions within toxicity limits and the apparent cure of the animal. This, however, does not appear to have been checked by lymph-node re inoculation studies, etc. The tartrobismuthate was selected as the salt of lowest toxicity for use in man, its administration being limited to intramuscular injection of an aqueous solution. Subcutaneous injection is undesirable and intravenous injection absolutely contraindicated. Sazerac and Levaditi concluded that the time is still too short to decide the ultimate sterilizing power of the drug, but they feel that it ranks with the best spirillicides now available. Its action is more intense than that of mercury, but slower than that of the most active arsenicals. Its stability *in vitro* is a point of importance. Fournier and Guénot have employed sodium-potassium tartrobismuthate in oil suspension in approximately 200 syphilitic patients. They report the disappearance of the *Spirochæta pallida* from primary lesions by the day following the first injection; erosive chancre heal within a few days. They mention especially its ability to prevent relapse in patients who have failed to respond to arsenical and mercurial treatment. The dosage employed for injection is 20 to 30 eg. to a total dose of 2 to 3 gm. in a series of ten to twelve injections at five- to seven-day intervals, given intramuscularly. The complications observed consisted of local reactions at the site of injection and the practically invariable appearance of a bismuth line in the gums, with dark patches on the mucous membranes. Stomatitis is occasionally observed. The drug can be recovered from the blood and spinal fluid and is eliminated in the urine, the feces, the bile, the saliva and the sweat. The action upon mucous recurrences impressed these authors as especially favorable. The Wassermann reaction responds by complete reversal from positive to negative; in most cases in one course, and in occasional instances after two courses. MARIE and FOURCADE, reporting on 40 cases (*Ann. de l'Inst. Pasteur*, 1922, 36, 34), state that the results obtained

in general paresis are *nil*, but that in localized neurosyphilitic processes the effect is more favorable. LÉVY-BING, GERBAY and PHILLIPREAU (*Ann. d. mal. vener.*, 1922, 17, 174) direct attention to the rapid effect of the tartrobismuthate on visible lesions, adopting, however, the disputable point of view that the disappearance of visible lesions is the best criterion of therapeutic effectiveness. They direct attention to the renal reactions to the drug and the rapid onset of signs of intolerance on the part of the mucous membranes. Bad oral hygiene particularly predisposes to bismuth stomatitis, and, with the pigmentation, may be so marked as to betray the patient's condition to others. MILIAN and PERIN (*Bull. Soc. franc de dermat. et syph.*, 1922, 29, 7) discuss the clinical and pathologic characteristics of bismuth stomatitis. The stomatitis disappears within fifteen days after treatment is discontinued. HUDELO, BORDET and BOULANGER-PILET (*Bull. Soc. franc de dermat. et syph.*, 1922, 29, 10) and JEANSELME, *et al* (*Ibid.*, p. 13) found stomatitis to occur in 30 to 40 per cent of cases. Intravenous injection of even minute amounts, as a result of hemorrhage around the needle-point in intramuscular injection, may result in death.

---

**Arsphenamine Prophylaxis of Syphilis.**—The use of arsenicals in the prophylaxis of syphilis during the primary incubation period, continues to be a subject of discussion. NICOLAU (*Ann. d. mal. vener.*, 1922, 17, 161) reports 2 cases, in the first of which a pregnant woman had been exposed through intercourse with her husband at frequent intervals for a period of ten days, while he had an active primary lesion on the penis, in which numerous *Spirochaeta pallida* were demonstrated by dark field. The woman was given a total of 2.1 gm. of neoarsphenamine in twenty-three days, the first injections being separated by intervals of two, five and seven days. She was delivered at term of a living child. Neither she nor the infant have at any time shown any clinical or serologic evidence of the disease, in spite of the practical certainty of infection had prophylactic treatment not been given. The second case is that of a healthy mother, whose infant developed a chancre of the lip from an infected wet-nurse. The healthy mother suspecting the condition of the wet-nurse, resumed the nursing of her child during the period of development of the child's primary lesion of the lip. For eighteen days the infant, with a lesion on the lip swarming with *Spirochaeta pallida*, was regularly nursed by the healthy mother. The state of affairs was then discovered and the mother given injections of 0.45, 0.6, 0.75 and 0.75 gm. of neoarsphenamine, a total of 3 gm. in thirty-one days. No sign of syphilitic infection was present in the mother at the time the prophylactic treatment was begun, and she was observed for five weeks after it was discontinued without any manifestations. Nicolau feels, therefore, that the time limit for the application of prophylactic treatment in the pre-chancrous stage of syphilis can be materially extended with good results. GOLAY (*Ann. d. mal. vener.*, 1922, 17, 401), on the other hand, reports 2 cases in which prophylactic treatment, administered to patients later than fifteen days after exposure, failed to prevent the infection. These patients each received three much smaller injections of neoarsphenamine. He concludes that fifteen days is the latest interval after exposure at which any prophylactic effect may be looked for.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

**A Comparative Study of Normal and Malignant Tissues Grown in Artificial Culture.**—DREW (*Brit. Jour. Exper. Path.*, 1922, 3, 20) conducted a series of experiments to ascertain the behavior of mouse embryo heart, adult mouse heart and mouse sarcoma in rat plasma and in a salt mixture in which the calcium was present in a colloidal state. It was found that the various tissues and tumors fell into three divisions; embryonic tissues which grow vigorously in a plain plasma medium; tumors which also grow but to a lesser degree than embryonic cells; and adult tissues which show little or no growth. Two factors seemed necessary for the continued growth of tissues *in vitro*—a saline solution in which the calcium salts were probably in colloidal state and some substances contained in an extract of embryonic cells. The author was able to support the conclusions of Carrel and Ebeling that “the indefinite multiplication of cells in a medium is due entirely to substances contained in embryonic juice.” While continued growth was readily obtained in the living animal, early degeneration and death *in vitro* necessitated frequent subculture if even a limited growth was to be obtained. The experiments showed that this early death of cells depended upon an elaboration of toxic substances which quickly reach a lethal concentration. There was found to be a close biological relation between tumor parenchyma and stroma. The stroma of a transplanted tumor behaved in culture like an embryonic tissue rather than like that of an adult. The presence of stroma elements, although not necessary for the growth of parenchyma *in vitro*, exerted a profound influence upon it, and partly determined the degree of differentiation reached by the tumor cells.

**Comparative Study of the Wassermann and Sachs-Georgi Reactions.**—Much has appeared recently upon the value of the Sachs-Georgi reaction in the serodiagnosis of syphilis and conflicting results have been reported by various investigators (see *Am. Jour. Med. Sci.*, 1921, 162, 776). Recently D'AUNOY (*Jour. Med. Research*, 1921, 42, 339) gives a comprehensive history of the subject and reports comparative findings on 2150 sera. In addition to the classic Sachs-Georgi reaction, modifications were performed by using two different reagents, made by the addition in 1 case of 0.1 of 1 per cent sodium glycocholate and in the other case of 0.1 of 1 per cent sodium taurocholate to the cholesterinized extracts, the latter being discarded early in the work on account of its unreliability. The original Wassermann

reaction, employing beef-heart extract antigen and cholesterin reinforced, was performed in all instances. Identical results were obtained in 98.07 per cent of tests with the original cholesterin extract and in 95.91 per cent with the sodium glycocholate reinforced extract. In only one instance was the Sachs-Georgi reaction negative and the Wassermann test positive. All sera showing spontaneous flocculation with the Sachs-Georgi technic gave "anticomplementary results" with the Wassermann. A slightly increased number of positives was obtained by the use of the modified sodium glycocholate reagent. In 40 febrile cases no false positive results were obtained. The author concludes that "Due to its simplicity and apparent reliability, the precipitation test proposed by Sachs and Georgi for the serum diagnosis of syphilis appears to be a valuable addition to laboratory methods."

---

**Precipitins and the Etiology of Serum Sickness.**—WYARD (*Jour. Path. and Bacteriol.*, 1922, 25, 191) conducted observations on the sera of 51 men, who had received a previous injection or injections of horse serum, in an attempt to demonstrate the presence of precipitins in the blood of individuals suffering from serum sickness. The human serum was put up against a series of dilutions of horse serum (antitetanic serum), ranging from 1 to 10 to 1 to 1,000,000. In most cases the patient's serum was inactivated by heat for ten minutes at 55° C. The tubes were generally incubated at 37° C. for two hours and stood overnight at laboratory temperature, the results being read next morning. Sera from 6 men, who had never received any serum injection, gave negative results. The 51 cases were examined seventy-six times and precipitins were found in 25 of these thirty-nine times and was absent from the others on thirty-seven occasions. Eliminating those cases which did not present symptoms of serum sickness at the time of examination, out of 36 suffering with serum sickness the blood of 24 contained precipitins to horse serum. The character of the rash did not afford any indication as to the presence or absence of precipitins. After one injection of horse serum precipitins could be found as long as from five to eight days, and sometimes persisted for at least fifty-nine days. A clearer view as to what actually was occurring could be gotten when the penultimate, rather than the last, injection was taken into account. The author concludes that "Serum disease is sometimes accompanied by the presence of precipitins in the blood of the patient, but the disease has no demonstrable relation with them; that the factors involved in the production of precipitins in human beings are the same as for experimental animals and that the antigenic properties of horse serum vary with the source of the serum."

---

**Effect of Time Between Obtaining a Spinal Fluid and Making a Cell Count on the Result of the Count.**—It is inferred from the literature on the subject, as a rule, that the cells in cerebrospinal fluid must be counted immediately after the lumbar puncture. While this is evidently true in many cases of marked meningeal irritation, there is a paucity of proof that immediate counting is necessary in normal spinal fluids or those with moderate pleocytoses, as found in

a large number of tabetics and neurosyphilitics. In order to throw some light on the subject, WYNN (*Jour. Lab. and Clin. Med.*, 1922, 7, 273) counted the cells of eighty spinal fluids at varying intervals up to fifteen hours after lumbar puncture, using a Levy double counting chamber and counting the cells in 18 sq. mm. in each case. Between counts the first forty fluids were kept in the ice-box and the second forty were allowed to remain at room temperature. It was found that the cells in clear spinal fluids collected in clean tubes and tightly stoppered could be safely counted, when thoroughly mixed, at any time up to at least fifteen hours if the fluid did not show a pellicle, sediment or web in the gross. There was no consequential difference in the counts of the fluids kept in the ice-box or at room temperature. "In 2 cases of meningitis the thorough mixture of small quantities (0.2 to 0.5 gm. for 6 cc) of powdered sodium citrate with the fluids made it possible to duplicate the original cell counts (within the limit of technical error) at three- and fifteen-hour intervals." The author concludes that this "procedure must be tried" in a large series of cases before any conclusions are warranted regarding such citrating of fluids.

---

**The Thermal Death Point of the Spores of *Bacillus Botulinus* in Canned Foods.**—WEISS (*Jour. Infect. Dis.*, 1921, 29, 362) studied the heat resistance of the spores of *Bacillus botulinus* which were introduced, experimentally, into thirty-six varieties of standard brands of canned foods in the American market. To 9 parts of the food fluid was added 1 part of a month-old strain of *Bacillus botulinus* in a test-tube which, after thoroughly mixing, was sealed off and submerged in a de Khotinsky oil bath for varying periods of time at various temperatures. After exposure to the heat the tube was opened, 10 cc of freshly heated glucose agar were added and the mixture was incubated at 37.5° C. for at least three months. The size of the container being constant, it was found that at least two primary factors determined the length of exposure and the heat required to accomplish sterility: (1) The hydrogen-ion concentration; and (2) the physical character or consistency of the food. The more acid foods, such as canned fruits, require a maximum of fifty minutes at 100° C., thirty minutes at 105° C., or fifteen minutes at 110° C., whereas the vegetable products, being less acid, required from ninety to one hundred and eighty minutes at 100° C., thirty to seventy minutes' exposure at 105° C., or ten to twenty minutes' exposure at 110° C. The more fluid products required a shorter period of exposure at a given temperature than the less fluid ones. The heavier the syrup, the longer the period of exposure required at any one temperature. The author cautions that the temperatures and times of exposure in this paper are not to be directly applied to practical canning.

---

**Experimental Measles in Rabbits and Monkeys.**—In order to test the receptivity of rabbits to the infection of measles, NEVIN and BITTMAN (*Jour. Infect. Dis.*, 1921, 29, 427) inoculated the blood of 6 patients with measles into as many rabbits. Three of the rabbits received blood drawn on the second day, 2 rabbits received blood drawn on the third and 1 blood drawn on the fourth day after the onset of the disease. In all, 17 rabbits were inoculated, the other

11 receiving blood of rabbits that gave evidence of reaction. Inoculations were given intravenously in amounts varying from 1 to 15 cc. All the rabbits inoculated with human blood gave evidence of reaction, as did all, save 2, of the rabbits subinoculated from these 6 rabbits. Passage from 1 human case of measles was carried on through 5 rabbits, and a monkey inoculated with the blood of the fifth rabbit gave typical symptoms of measles. Fifteen rabbits developed symptoms in from three to seven days. The symptoms were not so marked as in monkeys. In some cases there was a rise in temperature, coincident with a decrease in the total leukocyte count, but this was by no means constant. Ten rabbits developed small hyperemic, slightly elevated spots on the labial mucosa, 5 of which had whitish centers. Twelve rabbits developed a marked conjunctivitis in from two to four days. "In no instance was a distinctly typical exanthem noted," but all of the 15 rabbits desquamated, beginning from the fifth to the fourteenth day. Aërobic and anaërobic cultures made of blood prior to inoculation showed no evidence of growth. Blood from cases other than measles failed to produce evidence of infection when inoculated into rabbits.

---

## HYGIENE AND PUBLIC HEALTH

---

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,  
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,  
WASHINGTON, D. C.

---

**Physiological Action of Light.**—CLARK (*Physiol. Rev.*, 1922, 2, 277) states that the first systematic effort to study the biological effects of light, and its therapeutic uses, was made by Finsen when he founded his Light Institute in Copenhagen in 1896. Much valuable work, both theoretical and practical, has been done there since, with especial success on the therapeutic side, in the treatment of lupus, but the fundamental problem of the mode of action of light on the living cell remains unsolved. Recently, the rapidly accumulating clinical results of light treatment in tuberculosis, rickets, malaria, etc., closely related as they are to the results of roentgen-ray and radium treatment, continually emphasize the importance of this problem and increase its mystery. It is at first disappointing to find that there is, apparently, in the animal kingdom no effect analogous to the action of light on the chlorophyl system of the green plant, by means of which light energy is stored and oxygen restored to the atmosphere. Although there is a universal conviction that sunlight is healthy, it is certain that people and animals can live a long time in darkness without any noticeably bad results. Blessing, who acted as physician to Nansen during his expedition in the *Fram*, published a report showing that members of

the party exhibited no evidence of anemia during the trip. More recently, Grober and Sempell examined horses that had worked for years in coal mines and found no anemia in any case where a satisfactory nutritive condition existed. But, though the physiological effect of sunlight seems at first sight indefinite and of dubious importance, the action of far ultraviolet light on normal tissue, and the action of near ultraviolet and visible light under certain pathological conditions, has been investigated enough to show that there are well-defined effects due to light, closely related to the physiological results of exposure to radium and roentgen rays. These results are gradually assuming considerable importance in clinical medicine and present theoretically an interesting but illusive problem in physiology. The rest of the article is given over to a discussion of the effect of light on microorganisms, on the eye, on the skin, muscles, blood and metabolism. It also considers photodynamic sensitization, heliotherapy and a theory of light action. The review is a model of critical excellence, clarity and completeness.

**Demonstration of Lepra Bacilli by Aspiration of Nodules.**—GREENBAUM and SCHAMBERG (*Jour. Am. Med. Assn.*, 1922, 78, 1295) state that in suspected cases of leprosy it is a common procedure to excise a nodule for microscopic study, but this, for various reasons, cannot always be done. Another method of searching for bacilli in the nodules is to scrape off the epidermis over a suspected nodule and make smears from the serum which exudes. This is satisfactory for dermic nodules, but for hypodermic infiltrations the procedure is less simple and is likely to draw blood. Characteristic lepra bacilli may be demonstrated in smears by acupuncture of lesions, a method which is simple, virtually painless and easy to carry out in timid and apprehensive patients. The technique consists in the use of a syringe with tightly fitting plunger, a small record syringe by preference, a short-pointed needle of average gauge and a few drops of salt solution or distilled water. The node is first gently massaged in order to bring as much fluid into it as possible. The needle is then introduced, after careful cleansing of the cutaneous surface, and the salt solution or distilled water slowly injected and withdrawn several times, thus making a sort of emulsion of the tissue about the needle point. The needle and its contents are then withdrawn, and smears are made from the fluid. This mode of diagnostic acupuncture is a simple and valuable aid in the diagnosis of leprosy. There are very few lesions of the skin which are likely to yield acid-fast bacilli. In lupus vulgaris bacilli are so sparse that they are with difficulty demonstrable by sectioning and staining. It has been shown that lepra bacilli in enlarged subcutaneous lymph nodes may be demonstrated by this method, and this may be of particular value in macular leprosy. The successful finding of *Spirochaeta pallida* in lymph glands by this technique is well known.

**Notice to Contributors.**—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, providing the request for them be written on the manuscript.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.



# INDEX.

## A

ACIDOSIS, alkalies in, 915  
 Actinomycosis, human, 759  
 Adenoid cystic epitheliomas, 452  
     operation, 884  
 Abdominal membranes, 608  
 Agglutination in toxic effects of arsenphenamine, 604  
 Albuminuria, orthostatic, 742  
     in pregnancy, 300  
 Alkalies in acidosis, 915  
 Amebiasis of the bones, 450  
 Amebic colitis, 587  
 Amniotic liquid in preservation of fetal life, 919  
 Anemia, pernicious, 133  
 Angina pectoris, 912  
 Anorexia, gastric findings in children with, 763  
 Antibodies, pneumococcic, in lobar pneumonia, 832  
 Antimeningococcus serum, introduction of, by cistern puncture, 66  
 Apoplexy, thymus, 761  
 Arsphenamine, 452  
     neurorecurrences following, 449  
     prophylaxis of syphilis, 924  
 Arthropathy, chronic, 454  
 Artificial culture, normal and malignant tissues grown in, 925  
 Aschner, P. W., aseptic infarction of the kidney, 386  
 Asthma, 448  
     and hay fever, treatment of, 97  
     in infancy, 916  
 Atropine in fibrillation of the auricles, 1  
 Auricles, actions of atropine in fibrillation of, 1  
     of quinidine in fibrillation of, 1  
 Auricular fibrillation, 157  
     flutter, 656  
 Auriculoventricular bundle, block of the branches of, 469  
 Auster, L. S., studies in physiology of the gall-bladder, 345

## B

BACILLUS botulinus in canned foods, 927  
     lactimorbi in cats, 308  
 Backache, syphilitic, 109  
 Bacteria, elimination of, from the respiratory tract, 851  
 Bacteriology of blood of dogs, 311

Bacteriology of the infant's urine, 140  
 Barlow, R. A., study of vestibular nerve function in myxedema, 401  
 Berg, B. N., blood in chronic nephritis, 88  
 Beriberi, 227  
 Bernhard, A., chemical changes of the blood during immunization, 361  
 Biliary tract, disease of, 44  
 Bismuth salts in syphilotherapy, 922  
     in treatment of syphilis, 755  
 Bladder, exstrophy of, 453  
     hernia of, 757  
     tumor of, 137  
 Blanton, W. B., orthostatic albuminuria, 742  
 Block of the branches of the auriculoventricular bundle, 469  
 Blood cholesterol in syphilis, 604  
     in chronic nephritis, 88  
     diseases of childhood, 613  
     effect of radiation on, 768  
 Blood-pressure in hypertension, 604  
 Blood-sugar after removal of the liver, 603  
     in relation to neoplasia, 772  
 Bloomfield, A. L., mechanism of elimination of bacteria from the respiratory tract, 854  
 Botulinus toxin, 289  
     in contaminated foods, 624  
 Botulism, 253  
     from cheese, 151  
 Brachial plexus injuries, 606  
 Breast feeding, case records in, 915  
 Briggs, Le Roy H., bacterial endocarditis as a sequel to syphilitic valve defect, 275  
 Brown, C. E., total and differential leukocyte counts, 553  
 Brown, P. W., syphilitic patients whose chief complaint was stomach trouble, 867  
 Buchanan, J. A., phenomena of Raynaud's disease, 14

## C

CANCER of the cervix, 306  
     delay in treatment of, 712  
     mortality, 309  
     of prostate and seminal vesicles with radium, 136  
 Carbon are light in rickets, 456  
     tetrachloride, 623

Carbonated water and carbonated beverages, 154  
 Carcinoma of esophagus, 340  
   or prostate, 137  
 Cardiorenal diseases, 808  
 Carey, H. W., defective interventricular septum of the heart, 684  
 Carr, J. G., carcinoma of the esophagus with perforation of the aorta, 340  
 Cecil, R. L., etiology of pneumonia, 58  
 Cervix, cancer of, 306  
 Cesarean section, 144, 458, 920  
   rupture of the scar of a previous, 146

Chemotherapy of the typhoid carrier condition, 152

Chest of the child, 455

Chick embryo tissue, 310

Childhood, blood diseases of, 613  
   contagious diseases in, 610

Children born by Cesarean section, after-history of, 920  
   food requirements of, 611, 762  
   nephritis in, 296

Cholecystectomy, cystic duct in, 292

Christian, T. B., treatment of syphilis among the insane, 529

Colitis, amebic, 587

Colostrum, function of, 142

Compensation, mechanism of, 911

Complement-fixation tests in tuberculous infections, 771

Conner, L. A., experience in hospital with serum-free solution of pneumococci antibodies, in lobar pneumonia, 832

Cotton, H. A., infection of gastrointestinal tract in relation to systemic disorders, 329

Craig, H. R., congenital absence of the spleen, 703

Creatinuria, male sexual gland in prevention of, 222

Crohn, B. B., studies in physiology of the gall-bladder, 345

Crowell, B. C., neuritis in the tropics, 227

## D

DEATH, intrauterine, 614  
   point, thermal, 927

Deaver, J. B., clinical observations and research work, 901

Delinquent, the, 468

Diabetes, 479

  insipidus, pituitary extract in, 290

Diabetic diets (Woodyatt), 289

Diabetics, divided meals for, 291

Digitalis, absorption of, in man, 756

  in auricular fibrillation and flutter, 157

  emetic action of, 291

Diphtheria carriers among school children, 308

  mortality, 467

  toxin-antitoxin in public schools, 610

Downs, T. McK., Wassermann reaction in nonlucetic cases, 514

Draper, J. W., infection of gastrointestinal tract in relation to systemic disorders, 322

Drug poisoning, 253

Duodenectomy, 293

Duodenum, congenital obstruction of, 454

## E

EBRIGHT, G. E., epidemic encephalitis, acute poliomyelitis, botulism and food and drug poisoning, 253

Eek fistula in dogs, 311

Eclampsia post partum, 461

Eczema in breast-fed infants, 297  
   in infancy, 916  
   infantile, 915

Elephantiasis vulvæ, 617

Empyema, tuberculous, 759

Encephalitis, epidemic, 253

Endameba dysenteriae in Hodgkin's disease, 450

Endocarditis, bacterial, 275

Endocrine glands, functions and interrelations of, 646

Endocrinology, 625

Epididymitis, 452

Epithelioma of the genito-urinary organs, 757

Erythrocytes, length of life of transfused, 134

Esophagus, carcinoma of, 340  
   digestion of, 464

## F

FARR, C. E., delay in treatment of cancer, 712

Fat of adipose tissue in disease, 772

Faught, F. A., functions and interrelations of the endocrine glands, 646

Fetal life, preservation of, 919

Fetterolf, G., safeguarding of the tonsil and adenoid operation, 884

Fever in early life, cause of, 916  
   glandular, 781  
   scarlet, 917

Fibroblasts, ten-year-old strain of, 448

Flutter, 157

Food poisoning, 253

Fordyce, J. A., syphilis from a clinical and biologic point of view, 492

Forearm fractures, 292

Formol reactions, 309

  and Wassermann, comparison of, reactions in diagnosis of syphilis, 152

Foster, N. B., relations of hypertension to cardiorenal disease, 808  
Fractures, treatment of, 293

## G

GALACTOCELE, 459  
Gall-bladder, physiology of, 345  
Gastric ulcer, treatment of, 451  
Gastroenterostomy, 135  
    best technic for, 209  
Gastrointestinal tract in systemic disorders, infection of, 313, 322, 329  
Gastrosplasm, 188  
Germanium dioxide, erythropoietic action of, 462  
Gestation, 460  
Goiter, exophthalmic, radium in, 605  
Gonococcal infections, 307  
Gonococcus infections, 307  
Grape-sugar as a stimulant to labor pains, 143

## H

HAFT, H. H., cecal tuberculosis with pulmonary tuberculosis, 115  
Hajek, J., auricular flutter, 656  
Hanford, C. W., carcinoma of the esophagus with perforation of the aorta, 340  
Hanford, J. M., roentgen-ray diagnosis of tuberculous cervical lymph glands, 539  
Hay fever and asthma, treatment of, 97  
Health and heart disease, 819  
Heart, diastolic activity of, 756  
    disease in children, 141  
    *pregnancy complicating*, 847  
    vital capacity in, 819  
    in hypertension, 914  
    interventricular septum of, 684  
    in mothers and the newborn, 612  
Height and length in school-boys, 298  
Held, I. W., gastrosplasm, 188  
Hematuria, essential, 136  
Hemolytic streptococci, 605  
Hemorrhage complicating pregnancy, 764  
    from ruptured corpus luteum, 304  
Hemosiderosis of pernicious anemia, 133  
Hepatic extract, effect of, on cardiovascular apparatus, 448  
Hernia of the bladder, 757  
Herrick, J. B., block of the branches of the auriculoventricular bundle, 469  
Hirschboeck, F. J., massive collapse of the lungs, 268  
Hookworm control measures on soil pollution, 778  
    disease in a cacao estate, 779  
    control of, 776  
    relation of domestic chicken in spread of, 777

Hookworm, dissemination in domestic pig, 778  
    larvæ in soils, apparatus for isolating, 777  
    finding of unsheathed, 777  
    infective, 780  
    length of life of, 779  
    migration of, 779  
    position of infective, 779  
Hypertension, heart in, 914  
Hypophysectomy in dogs and cats, 290  
Hysteropexy, 460

## I

IMMUNIZATION, changes of the blood during, 361  
Infant feeding, 139, 140  
    in country practice, 763  
Infantile eczema, 915  
Influenzal meningitis, 919  
Inlow, W. De P., the spleen and digestion, 29  
Inlow, W. De P., the spleen in inanition, 173  
Insane, syphilis among the, 529  
    treatment of the, 338  
Interventricular septum of the heart, 684  
Intestinal obstruction, 758

## J

JOINTS, synovial membrane, tumors of, 136  
Jones, W. C., total and differential leukocyte counts, 553

## K

KAHN, M., biochemical studies in diseases of the skin, 379  
Keating, J. H., auricular flutter, 656  
Kidney, aseptic infarction of, 386  
    decapsulation of, in Bright's disease, 450  
    infections of, 607  
    nontuberculous, 758  
    test, urea, 913  
Kilduffe, R. A., comparison of the Sachs-Georgi Wassermann reactions in the serologic diagnosis of syphilis, 523  
Kilduffe, R. A., Wassermann test in prenatal and congenital syphilis, 677  
Krehbiel, O. F., chemical changes of the blood during immunization, 361

## L

LABOR complicated by infected fibroid, 615  
    induction of, with castor oil and quinine, 615  
Leg fractures, 292

Lepra bacilli, demonstration of, by aspiration of nodules, 929  
 Leukemia, three cases of, in one family, 545  
 Leukocyte counts, 553  
 Leukocytes, activity of, 621  
 Levin, O. L., biochemical studies in diseases of the skin, 379  
 Levy, I. H., cecal tuberculosis with pulmonary tuberculosis, 115  
 Lewis, B. G., application to other institutions of the results of treatment of the insane in Trenton State Hospital, 338  
 Lewis, T., actions of atropine and quinine in fibrillation of the auricles, 1  
 Lewis, T., digitalis in auricular fibrillation and flutter, 157  
 Light, physiological action of, 928  
 Livers, icteric, changes in, 774  
 Longcope, W. T., infectious mononucleosis (glandular fever), 781  
 Lung abscess, 428  
     suppuration, 452  
 Lungs of children, 142  
     collapse of the, 268  
     resection of, 453  
 Lymph glands, diagnosis of tuberculous, 539

M

McGAVRAN, C. W., three cases of leukemia in one family, 545  
 McLean, S., congenital absence of the spleen, 703  
 McNeal, M. D., male sexual gland in prevention of creatinuria, 222  
 Measles, experimental, in rabbits and monkeys, 927  
 Medical service for the small plant, 156  
 Megacaryocytes in the circulation, 603  
 Meningitis, influenzal, 919  
 Meningococcus strains, 468  
 Metabolism, basal, of prematurity, 918  
     of infants fed on dry milk powder, 299  
     of surviving mouse tissues and tumors, 774  
 Milk ingestion, 612  
     pasteurization, 150  
 Miller, F. P., exercise in the tuberculous, 263  
 Miller, N. C., prognosis in tuberculous lesions of the right and left lungs, 82  
 Mitchell, A. Graeme, introduction of antimeningococcus serum by cistern puncture, 66  
 Mononucleosis, infectious, 781  
 Musgrave, W. E., neuritis in the tropics, 227  
 Myers, C. N., syphilis from a clinical and biologic point of view, 492  
 Myohypertrophy, arterial, 911  
 Myxedema, study of vestibular nerve function in, 401

N

NEGRI bodies in the salivary glands in rabies, 312  
 Neoarsphenamine, 452  
     and neosalvarsan, action of, on leukocytes, 621  
 Nephrectomy, pregnancy after, 921  
 Nephritis in children, 296  
     chronic, 88  
     war, 605  
 Nerves, cranial, central and peripheral involvement of, 727  
 Nervous system, diseases of, 715  
 Neuman, L., treatment of typhoid fever by transfusion with artificially immunized blood, 690  
 Neuritis in the tropics, 227  
 Neurofibromyxoma treated by conservative operation, 138  
 Newborn infants, food requirements in, 762  
     pneumonia in, 302

O

OSTEITIS fibrosa, 292  
 Osteomalacia, 302  
 Ovarian autotransplantation, 147  
     tumors, histogenesis of, 303  
 Oxygen therapy, 914

P

PANCREAS, internal secretion of, 463  
     post-traumatic calcification of, 479  
 Pardee, H. E. B., pregnancy complicating heart disease, 847  
 Parotitis, secondary, 607  
 Pellagrin, breast-fed, 297  
 Peritoneal cavity, absorption from, 307  
 Physiology of the gall-bladder, 345  
 Pituitary extract in diabetes, 290  
     insipidus, 290  
     in exciting labor pains in pregnancy, 921  
 Placenta previa, treatment of, by abdominal hysterectomy, 460  
 Pneumonia, Bacillus influenza in nose and throat in, 622  
     etiology of, 58  
     lobar, 622  
     in the newborn, 302  
     streptococcus, 311  
 Pneumothorax, therapeutic, 428  
 Poliomyelitis, 457  
     acute, 253  
 Pratt, J. H., observations on the vital capacity in health and heart disease, 819  
 Precipitins and etiology of serum sickness, 926  
 Pregnancy after disease of ovaries and tubes, 143  
     nephrectomy, 921

- Pregnancy, albuminuria in, 300  
 blood-pressure in, 617  
 hemorrhage complicating, 764  
 labor pains in, 921  
 toxemias of, 614  
 twin, 616  
 Prematurity, basal metabolism of, 918  
 Prophylactic value of pertussis vaccine, 298  
 Prostate, carcinoma of, 137  
 enlargement of, 608  
 Prostatectomy, suprapubic, 452  
 Protein in disease processes, studies on, 621  
 injections, effects of, upon infections, 622  
 Pylorospasm in infants, 299

## Q

- QUINIDINE in fibrillation of the auricle, 1  
 Quinine in cardiac disease, 447

## R

- RABBITS, coliform infection in, 775  
 Rabies, 312  
 Radiation versus surgery in uterine cancer, 148  
 Radium in exophthalmic goiter, 605  
 treatment of benign bleeding, 619  
 of cancer of prostate, 136  
 Raynaud's disease, phenomena of, 14  
 Red blood cells, diurnal variation in sizes of, 773  
 Reed, A. C., diagnosis and treatment of amebic colitis, 587  
 Reilly, J. J., introduction of antimeningococcus serum by cistern puncture, 66  
 Reimann, S. P., clinical observations and research work, 901  
 Relapsing fever, Wassermann reaction in, 464  
 Research work, 901  
 Reviews—  
 Bland-Sutton, Tumors, 130  
 Bourne, Midwifery, 129  
 Bundy, Health of Jesus, 596  
 Byam and Archibald, Medicine in the Tropics, 445, 907  
 Clarkson, Venereal Clinic, 602  
 Cobb, Aids to Organotherapy, 442  
 Cobb, Organs of Internal Secretion, 439  
 Crile, Thyroid Gland, 750  
 Cumner, Laboratory Methods, 282  
 Dobell and O'Connor, Intestinal Protozoa of Man, 752  
 Elliott, Glaucoma, 445  
 Ellis and MacLeod, Factors of Foods, 595  
 Emerson, Nutrition and Growth in Children, 129

- Reviews—  
 Ewing, Neoplastic Diseases, 284  
 Fuller, Science of Ourselves, 908  
 George and Leonard, Gall-bladder, 286  
 Ghosh and Das, Hygiene and Public Health, 124  
 Groves, Fractures, 285  
 Hare, Therapeutics, 124  
 Hargitt and Hargitt, General Biology, 905  
 Harrow, Glands in Health and Disease, 600  
 Hawes, Tuberculosis, 437  
 Head, Neurology, 601  
 Hill, Infant Feeding, 441  
 Houghton, Contributions from the Peking (China) Union Medical College, 440  
 Hudson, Aids to Medicine, 285  
 Hutchinson and Sherren, Treatment, 599  
 Hyman, Vertebrate Anatomy, 444  
 King, Influenza, 597  
 Lamson, Heart Rhythms, 127  
 Lane-Clayton, Hygiene of Women and Children, 125  
 Loeb, Proteins, 443  
 Lyle, Physiology, 441  
 May, Diseases of the Eye, 751  
 Mellish, Papers of the Mayo Clinic, 595  
 Mellish, Writing of Medical Papers, 442  
 Misch, Lehrbuch der Grenzgebiete der Medizin und Zahnheilkunde, 132  
 Papers from the Mayo Foundation, 282  
 Parker, Allied Senses in the Vertebrates, 598  
 Porter and Carter, Management of the Sick Infant, 439  
 Potter, Version in Obstetrics, 131  
 Prevention of Malaria in Federated Malay States, 287  
 Questions Neurologiques d'Actualite, 907  
 Roussy and Bertrand, Pathological Histology, 749  
 Ruffer, Palaeopathology, 125  
 Schieppegrell, Hayfever and Asthma, 749  
 de Schweinitz, Diseases of the Eye, 286  
 Shaw, Hyperpiesia and Hyperpiesis, 598  
 Simon, Clinical Diseases, 905  
 Simpson, Radium Therapy, 283  
 Singer, History and Method of Science, 753  
 Stelwagon and Gaskill, Diseases of the Skin, 128  
 Stevens, Practice of Medicine, 438

## Reviews—

- Stookey and Huber, Treatment of Peripheral Nerves, 283  
 Surgical Clinics of North America, 132, 286, 751  
 Sutton, Diseases of the Skin, 127  
 Thoma, Oral Roentgenology, 437  
 Travasso, Memorias do Instituto Oswaldo Cruz, 751  
 Turrell, Electrotherapy, 597  
 Van Blareom, Obstetrical Nursing, 444  
 Vaughan, Epidemiology and Public Health, 600  
 Walker, Dermatology, 284  
 Whitaker, Brain and Spinal Cord, 443  
 Wilde, Physiology of Gout, Rheumatism and Arthritis, 906  
 Williams, Opiate Addiction, 288  
 Willius, Electrocardiography, 130  
 Wilson, General Practice, 131  
 Wilson, Study of Disease, 598  
 Witherbee and Remer, Roentgen-ray Dosage in Treatment and Radiography, 906  
 Rieh, H. M., lung abscess treated by therapeutic pneumothorax, 428  
 Roemer, J., gastrospasm, 188  
 Roentgen-ray findings in normal chest of the child, 457  
 Rohdenburg, G. L., chemical changes of the blood during immunization, 361  
 Rosen, I., syphilis from a clinical and biologic point of view, 492  
 Rupture of the membranes, 766  
 Ryan, T. J., functions and interrelations of the endocrine glands, 646

## S

- SACHS, E., central and peripheral involvement of the cranial nerves, 727  
 Sachs-Georgi and Wassermann reactions in the serologic diagnosis in syphilis, 523  
 study of, 925  
 Sajous, C. E. de M., endocrinology as a key to the solution of modern medical problems, 625  
 Sarcoma of the long bones, 453  
 Satterlee, G. R., infection of gastrointestinal tract in systemic disorders, 313  
 Scarlet fever, 917  
 Schiek test, 775  
 School child, the, after tonsil and adenoid removal, 455  
 Serum sickness, precipitins and etiology of, 926  
 Short-circuiting operations, 607  
 Skin, biochemical studies in diseases of, 379

- Smallpox in twenty states, 624  
 Smith, Fred M., block of the branch of the auriculoventricular bundle, 4  
 Sources of salt in relation to health, 1  
 Spinal fluid, 926  
 Spleen, congenital absence of, 705  
 in inanition, 173  
 and pancreatic secretion, 26  
 ruptured, 138  
 Sporotrichosis, disseminated gummatous, 72  
 Stivelman, B. P., prognosis in tuberculous lesions of the right and left lungs, 82  
 Stokes, J. H., syphilitic patients whose chief complaint was stomach trouble, 867  
 Stomach, benign tumors of the, 135  
 Streptococci, hemolytic, 605  
 Streptococcus pneumoniae, 311  
 Surgeon, the, as a pathologist, 451  
 Syphilis among the insane, 529  
 arsphenamine prophylaxis of, 924  
 blood cholesterol in, 604  
 diagnosis of, in malarial subjects, 463  
 from a clinical and biologic point of view, 492  
 gastric, 608  
 Wassermann test in, 677  
 Syphilitic liver and heart, treatment of, 415  
 patients with stomach trouble, 867  
 Syphilotherapy, bismuth salts in, 923

## T

- TABLE utensils as sources of tuberculous infection, 155  
 Therapeutic value of pertussis vaccine, 298  
 Therapy, oxygen, 914  
 Thompson, W., syphilitic backache, 109  
 Thoracoscopy in surgery of the chest, 606  
 Thymus apoplexy, 761  
 Thyrotoxicosis, 137  
 Tonsil, safeguarding of, and adenoid operation, 884  
 Tooth development and preservation, 760  
 Toxemia of pregnancy and uterine sepsis, 146  
 Trichomonas, vaginalis vaginitis, 770  
 Trigeminal nerve, anatomy of, 606  
 Treponema pallidum, 312  
 Tubercle bacilli, destruction of, in sewage by chlorine, 156  
 Tuberculosis, abdominal, 609  
 of husband and wife, 153  
 prevention of, 780  
 treatment of, with the carbon-arc lamp, 609

- Tuberculous abscess of the chest wall, 609  
 exercise in the, 263  
 infection, 465  
 lesions of the lungs, 82  
 Tularemia in laboratory workers, 467  
 new disease of man, 134  
 Tumor of the bladder, 137  
 Tumors, surgery of thoracic, 573  
 Typhoid fever, treatment of, by trans-  
 fusion of artificial immunized blood, 690  
 Typhus fever, 310, 465  
 etiology of, 153

## U

- ULCER, duodenal, in infancy, 137  
 of lesser curvature of stomach, 138  
 Urea kidney test, 913  
 Urethral stricture in women, 149  
 Uterus, action of emetin hydrochloride  
 upon, 619  
 of salicylates on, 768  
 rupture of, 302, 616

## V

- VACCINATION, antirabic, by means of  
 desiccated virus, 150

- Vander Veer, A., treatment of hay fever  
 and asthma, 97  
 Vitamins, importance of, in bacterial  
 growths, 773  
 Von Recklinghausen's disease, 292

## W

- WARFIELD, L. M., disseminated gum-  
 matous sporotrichosis, 72  
 War nephritis, 605  
 Wassermann reactions, 309, 463  
 in nonluctic cases, 514  
 and Sachs-Georgi reactions, study  
 of, 925  
 test in syphilis, 684  
 Wells, H. G., post-traumatic calcifica-  
 tion of the pancreas with diabetes,  
 479  
 Wilensky, A. O., gastroenterostomy,  
 best technic for, 209  
 Wilensky, A. O., surgery of thoracic  
 tumors, 573  
 Wilensky, A. O., surgical aspects of  
 disease of the biliary tract, 44  
 Wile, U. J., treatment of syphilitic liver  
 and heart, 415  
 Williamson, R. T., vibrating sensation  
 in diseases of the nervous system, 715

